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Third Annual "Symposium on Advances in Cancer Treatment Research"

23rd Annual Clinical Conference on "Cancer of the Genitourinary Tract"

The Secretary of Health, Education, and Welfare has determined that the publication of this periodical is necessary in the transaction of the public business required by law of this Department. Use of funds for printing this periodical has been approved by the Director of the Office of Management and Budget through January 31, 1980.

Proceedings of the Osteosarcoma Study Group Meeting

Division of Cancer Treatment
National Cancer Institute

January 19, 1977
Bethesda, Maryland

Introduction: Treatment of Osteogenic Sarcoma

The Osteogenic Sarcoma Study Group first met in Bethesda, Md, in March 1972, under the auspices of the Cancer Therapy Evaluation Program. It initially learned about responses in this disease to high-dose methotrexate followed by citrovorum factor rescue as reported by Jaffe et al (1) using the method originally applied clinically by Djerassi et al (2). Adriamycin, then in widespread clinical testing, was also shown to cause tumor regression (3).

The demonstration of some responsiveness to chemotherapy of a very malignant tumor predominating in adolescents and young adults was followed promptly by its utilization in adjuvant fashion following primary surgical treatment of osteogenic sarcoma. Meetings held early in 1973 attempted to provide focus and increase collaboration in these studies. By 1974, several studies showing marked improvement in disease-free survival in patients treated with various regimens including either adriamycin (eg, Conpadri-I) or high-dose methotrexate were presented in a workshop at the yearly meeting of the American Society of Clinical Oncology in Houston, Tex (4–7). Over the ensuing years, results of the various series were published showing this improvement in relation to historical controls from the Memorial Hospital series of Marcove et al (8).

The enthusiasm generated from these results spurred the development of high-dose methotrexate regimens and improved their application and safety, as well as pharmacologic monitoring. In addition, a major effort to overcome the cardiotoxicity of adriamycin undoubtedly was partly based on the experience with this disease.

By January 1976, the Osteogenic Sarcoma Study Group's optimism was somewhat dampened by a substantial rate of relapse in spite of fine tuning in the initial regimens, and by the finding from the Mayo Clinic of an improvement in survival over the past decade in the absence of any adjuvant therapy (9). In the Mayo Clinic experience (10), a 40% disease-free survival at 2 years for cases of "classic" osteogenic sarcoma approached that obtained in some adjuvant series, and far exceeded the often quoted 20% rate of the Marcove series. The attention shifted to a much greater consideration of prognostic variables in this disease and to careful scrutiny of the ingredients for successful adjuvant programs. In fact, by this year's meeting, doubts on the success of the adjuvant programs were being increasingly expressed.

The 1977 meeting of the Group, therefore, was structured to look at prognostic variables, both pathologic and clinical, and at the essential parameters to consider in the design and interpretation of clinical trials. The papers of Dahlin (11), Simon (12), and Carter and Friedman (13) cover this topic. In addition, we reviewed newer surgical approaches as well as the efficacy of chemotherapy in this preoperative setting; this experience is recounted by Marcove at Memorial Hospital (14), Sim at the Mayo Clinic (15), Eilber at the University of California at Los Angeles (16), and Jaffe et al at the Sidney Farber Cancer Institute (17). An update on the adjuvant studies based on high-dose methotrexate or adriamycin follows and will receive additional comments in the concluding paper. Finally, new approaches to the chemotherapy of recurrent osteogenic sarcoma are presented. Dr. Goldin's presentation (18) outlined the experimental basis for the most common therapy: high-dose methotrexate with citrovorum factor rescue. The clinical experience with chemotherapy of metastatic osteosarcoma, strikingly small relative to the adjuvant effort, is summarized in papers by Von Hoff et al (19), Benjamin et al (20), Shepp et al (21), Levine et al (22), and Ochs et al (23), and is also alluded to in the many papers dealing with the adjuvant use of chemotherapy.

The deliberations held yearly by these investigators actively studying the treatment of osteogenic sarcoma represent an interesting example of the evolution of medical knowledge and clinical thinking. Publication of the studies seems warranted at this time: the lessons of the past and the directions of the future may be discerned at this juncture.

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Franco M. Muggia
Harry Handelsman

Osteosarcoma of Bone and a Consideration of Prognostic Variables

David C. Dahlin[1,*]

PROPOSED DEFINITIONS

Osteosarcoma of the bone is defined by the World Health Organization as a malignant tumor characterized by the direct formation of bone or osteoid tissue by tumor cells (1). The Armed Forces Institute of Pathology's (2) definition of osteosarcoma is "a malignant primary tumor of bone consisting of malignant stroma with evidence of malignant osteoid, bone, and/or cartilage formation." Jaffe (3) stated that "in general, an *osteogenic sarcoma* may be defined as a specialized connective-tissue sarcoma which forms neoplastic osteoid and osseous tissue in the course of its evolution." Lichtenstein (4) also indicated that neoplastic osteoid tissue of bone is a necessary product of an osteosarcoma although tumor cartilage may be a conspicuous cytologic feature in some instances. Aegerter and Kirkpatrick (5) stated that "osteosarcoma usually produces at least some osteoid but it is our contention that it need not, thereby allowing the inclusion in this class of a group of tumors whose cells have the appearance of osteoblasts and whose behavior is like that of osteosarcomas." I believe that to qualify as an osteosarcoma the proliferating malignant cells of the neoplasm must produce an osteoid substance or material histologically indistinguishable from it in at least small foci (6).

The consensus, therefore, is that osteosarcoma is a recognizable entity because of the matrix produced by the tumor cells. Tumors that fulfill this qualification may, as indicated above, show a preponderance of chondrosarcoma- or fibrosarcoma-like differentiation; a few even show a preponderance of cells like those of osteosarcoma but without demonstrable matrix. Currently, this categorization with only minor and unimportant exceptions is generally used. Many investigators have subdivided the osteosarcomas into osteoblastic, chondroblastic, and fibroblastic types because of the predominant differentiation discernible by the pathologist who examines specimens from these tumors. Essential to the diagnosis, however, is the presence of areas with osteoid production by the tumor cells.

MAYO CLINIC EXPERIENCE

Figure 1 shows the age and sex distributions of patients and the skeletal distribution of 962 osteosarcomas seen at the Mayo Clinic until December 31, 1975. The distributions are similar to those of many series described in the literature. One hundred and fifty-eight cases of unmixed fibrosarcoma of the bone, 470 cases of chondrosarcoma, and 15 cases of mesenchymal chondrosarcoma were not included in the foregoing data. Again, the numbers of these various sarcomas in relation to the total number of osteosarcomas are similar to those found in other studies of bone tumors in general.

Categories of Osteosarcoma Excluded From Statistical Analysis

One might consider the 962 tumors as "ordinary" osteosarcomas, but within this group there are six different categories of osteosarcomas which were excluded from a statistical appraisal of the results of treatment for ordinary osteosarcoma.

Data from a recent study (in preparation) of all 363 osteosarcoma cases seen at the Mayo Clinic between 1963 and mid-1974 are given as an illustration. These data are used because considerable effort was spent to confirm all cases and to correlate the pathologic changes with various clinical aspects of the disease, its treatment, and the patients' subsequent survival.

Osteosarcomas with first definitive treatment elsewhere (24%).—This group of osteosarcomas was not considered to be useful statistically because of the great variation in the type of definitive treatment that had been administered and because only survivors of the early risks of death could be referred to the Mayo Clinic.

Osteosarcomas with metastases when first seen (17%).—This category may be of value when one is attempting to assess the treatment modalities for metastatic osteosarcoma, but it is considerably different from the usual, localized form of disease in

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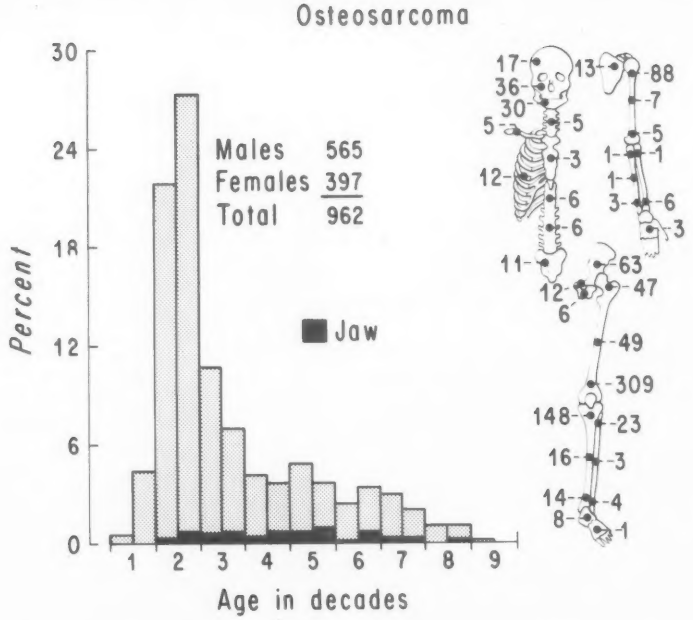

FIGURE 1.—Profile of cases of osteosarcoma seen at the Mayo Clinic until December 31, 1975. Note age and sex distributions of patients and skeletal distribution of the 962 tumors.

which a single lesion can be treated. Furthermore, the reasons for deciding to refer a patient to the Mayo Clinic because of the presence of metastases would introduce another variable of unknown characteristics. This 17% includes a very few patients who had synchronous multifocal osteosarcoma; their treatment is substantially different from that for the usual single osteosarcoma. Patients are usually "inoperable" when first seen.

Osteosarcomas of the skull and vertebrae and inoperable lesions of the pelvis (6%).—To exclude this group of osteosarcomas seems reasonable. These lesions may be completely inoperable from the surgeon's standpoint (unable to attain a total resection with an ample margin around the tumor). In those few osteosarcomas of the skull in which total resection can be achieved, it is usually with a minimal margin of uninvolved tissue.

Osteosarcomas of the jaws.—Sixty-six (7%) of the 962 osteosarcomas (only 4% occurred in the 1963–74 study) arose in either the mandible or the maxilla. Information on these sarcomas was not included in the survival data for several reasons. Although the surgeon may be able to resect the tumor completely, the circumscribed margins frequently are limited. Other important differences from ordinary osteosarcomas exist. The average grade (degree of differentiation) is usually lower (either grade 2 or 3 by Broder's method compared with grade 3 or 4 for ordinary osteosarcomas). Furthermore, an inordinate number of osteosarcomas of the jaws are predominantly cartilaginous. Because this chondroid quality is so profound, approximately half of the cases in some series are diagnosed definitively as chondrosarcomas. Finally, patients who have osteosarcoma of the jaws are, on the average, from 1 to 2 decades older than patients with osteosarcoma in the usual sites in the major tubular bones. Despite these appreciable differences from ordinary osteosarcomas, the survival is better for patients with osteosarcoma of the jaws than it is for those with osteosarcoma in the usual sites (7).

Radiation-induced osteosarcomas (4%).—As of January 1, 1976, 70 cases of sarcoma of the bone that arose after administration of irradiation for several reasons had been seen at the Mayo Clinic. Sixteen of these 70 patients were in the 1963–74 study. Of the 70 tumors, 35 were osteosarcomas. Statistically valid information about the curability of radiation-induced osteosarcomas is not available, but excluding this group from statistical analysis seemed necessary because several patients had two

different malignant lesions (eg, carcinoma of the uterus or breast and osteosarcoma). Sixty-three percent of the affected patients were > 40 years old.

Periosteal osteosarcomas (2% of the special study).—This rare tumor comprised only about 1% of the total of 962 osteosarcomas (8). This tumor is ordinarily relatively low grade, is predominantly cartilaginous, and occurs on the surface of a bone, especially the tibia. The available evidence indicates that this lesion is much more curable than is the average osteosarcoma; thus, inclusion of such cases would obviously alter the prognosis. Some have regarded this lesion as chondrosarcoma (1).

Types of Osteosarcoma Excluded From Overall Data

Parosteal (juxtacortical) osteosarcomas.—The 36 tumors of this type were not included in the overall data on osteosarcomas and obviously have not been included in the statistical analysis of the results of therapy for osteosarcoma (9). There were 11 such cases seen during the period covered by the 1963–74 study. These tumors characteristically are heavily ossified, are located on the surface of a bone, and are of extremely low grade. Most commonly, they are located on the posterior surface of the lower part of a femoral shaft. Evidence from many studies indicates a curability rate of 80%–90% for this relatively unusual type of sarcoma.

Dedifferentiated chondrosarcomas.—Among the 470 chondrosarcomas previously mentioned, 51 patients with a typically low-grade (well-differentiated) cartilaginous tumor had a superimposed high-grade sarcoma. We labeled these sarcomas as "dedifferentiated chondrosarcomas" (10), and they were excluded from our total osteosarcoma group even though definite osteosarcomatous differentiation in the highly malignant portions of the tumor was seen in 23. Six such osteosarcomas were encountered during the 1963–74 period. These osteosarcomas coexisting with chondrosarcomas obviously are different from the ordinary osteosarcomas. Almost 90% of the patients were > 40 years of age.

Osteosarcomas in extraosseous sites.—The relatively few osteosarcomas that arose in extraosseous sites (in the somatic soft tissues) were also excluded from this study.

Further Analysis

Within the definitive group of osteosarcomas from which survival data were calculated are two groups that require special mention. The first group, which comprises approximately 5% of the total number of osteosarcomas, consists of tumors with either large or small areas that prompt the arbitrary diagnosis of malignant fibrous histiocytoma (11). The tumor cells in these zones have a histiocytic quality: many of the nuclei are grooved, malignant giant cells are common, and many of the neoplastic cells contain at least small amounts of a lipid substance. Osteoid in these zones may be absent or minimal. Many of the tumors are rather standard osteosarcoma in part, and another part resembles malignant fibrous histiocytoma. In a few instances, the tumor throughout is exceedingly suggestive of the soft tissue entity we regard as malignant fibrous histiocytoma. Presently, it seems wise to continue to classify such tumors as osteosarcomas when osteoid can be found in only a small area and merely to make a note of their resemblance to malignant fibrous histiocytoma so that in the future the statistician may be able to determine whether a given modality of therapy is especially efficacious in this group. These were not segregated from the total group in the 1963–74 study.

The second group of cases, which comprises only about 2% of the total number of osteosarcomas, consists of what is now called telangiectatic osteosarcomas (12). These were not segregated from the total group in the 1963–74 study. Characteristically, this lesion appears to be completely lytic on the roentgenogram; the cut surface of the tumor is very bloody, and often the surgeon can find no viable malignant tissue except for a thin rim at the margin of the tumor. Spaces resembling those of aneurysmal bone cysts are usually found. The diagnosis of malignancy depends on the cytologic evaluation of individual tumor cells. Osteoid is usually sparse or even debatably present in these lesions. In our experience with 25 telangiectatic osteosarcomas from among the 962 osteosarcomas at the Mayo Clinic, 23 of the patients have died of their sarcomas. One patient has had high transfemoral amputation for this lesion in the distal part of a femur and has had operations twice for pulmonary metastases; there is only one long-term survivor.

A characteristic of osteosarcoma that has been documented adequately by others and authenticated in our own studies is that, even within the definitive group of osteosarcomas that can be subjected to statistical analysis, distinct differences in prognosis depend on the site of origin of the tumor. For example, many studies have shown that osteosarcomas of the femur are approximately two times as lethal as are osteosarcomas of the tibia. In addition, there is some indication that differences in age and sex affect the curability of osteosarcomas.

COMMENT

The foregoing is merely an acknowledgment that, after the pathologist has made the frequently difficult decision that a specific lesion is, in fact, an osteosarcoma, there are numerous clinically recognizable and sometimes pathologically distinct features that can be detected. These features certainly must be considered by the statistician charged with the responsibility of determining whether a proposed method of treatment is wise.

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Clinical Prognostic Factors in Osteosarcoma

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SUMMARY

Clinical characteristics thought to be of prognostic importance for patients with osteosarcoma are reviewed. The importance of considering prognostic factors in the evaluation of new therapies when no concurrent control group is available is emphasized.

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In the past several years exciting progress in the treatment of patients with osteosarcoma has been reported (1–3). The evaluation of these new combined-modality regimens has been based upon comparison to historical controls. Many investigators have felt that the new treatments are so effective for the selected patients studied that they cannot participate in randomized clinical evaluations of these regimens. Because of the toxicity, cost, and inconvenience to the patient of the new treatments, it is important to be as certain as possible that the new regimens offer improved therapeutic benefit. Hill (4) has extensively discussed pitfalls in the use of historical controls and has emphasized the need for demonstrating comparability of treatment groups with regard to prognostic factors for any therapeutic study. Gehan and Freireich (5) have defended the use of historical controls in certain situations, but have cautioned that it is essential "that the important patient characteristics related to prognosis are known so that comparable groups can be selected."

The identification of prognostic factors is therefore essential for the adequate evaluation of new therapies in studies performed without a concurrent control group. In addition, such knowledge will permit the enlightened selection of therapy and design of clinical trials for particular subsets of patients, and where randomized studies are feasible, prognostic variables may be utilized for the development of stratification procedures. For these reasons, understanding of prognostic factors for patients with osteosarcoma is of great importance today.

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RESULTS

Pathologic Type

A review of the literature for identifying clinical prognostic factors is made difficult by the nonstandard use of the term "osteogenic sarcoma." In this paper, we shall use "osteogenic sarcoma" and "osteosarcoma" interchangeably to refer approximately to the osteoid-producing bone sarcomas of Dahlin and Coventry (6), the osteogenic sarcomas of Marcove et al (7), and the osteosarcomas of McKenna et al (8). Some authors have combined chondrosarcoma, fibrosarcoma, and parosteal osteogenic sarcoma in their studies and have not adequately evaluated whether their findings or lack of findings with regard to clinical prognostic variables are due to correlations between clinical variables and histology of the tumors. This problem also arises when osteosarcomas in sites affected by Paget's disease are combined with the other cases. When some studies of clinical prognostic factors have been reevaluated, it has been found that cases of Ewing's sarcoma, lymphoma, and benign tumors had been included. MacDonald and Budd (9) classified as osteosarcoma only 12% of tumors earlier labeled osteogenic sarcoma in their study. As a result of these problems, there is no series both large enough and analyzed cleanly enough to adequately define the clinical variables of prognostic importance in the osteoid-producing osteogenic sarcomas. The literature does contain single variable analyses, but little information is available on interrelationships

among the variables or on the possibility that factors have independent effects on prognosis.

Extent of Disease

One factor thought to influence prognosis is the presence or absence of recognizable pulmonary metastases at the time of initial presentation of the patient. Sweetnam et al (10) reported that the average time between the recognition of pulmonary disease and death was 6 months, a much shorter time than the overall survival of the presenting patients. In most reports of large series, patients presenting with distant metastases have been either excluded or given palliative treatment. If the presence of distant metastases is an important factor, as it seems to be, then one must be very careful in comparing the results of different treatment studies which include only patients without recognizable distant metastases at presentation. McKenna et al (8) report that 10% of their patients presented with pulmonary metastases and 70% of the autopsies demonstrated pulmonary metastases. Sweetnam et al (10) report a median time to metastatic disease of 10 months. The fact that metastases are recognizable so soon after amputation in so many cases indicates that tumor foci in the lungs were present before removal of the primary tumor. Consequently, survival statistics obtained for patients without "recognizable" metastases at presentation may depend critically on the initial metastatic workup. The use of lung tomography in the initial workup may result in the selection of a greater proportion of potential cures as compared with previous studies where tomography was not used. The use of lung tomography in followup examination may tend to identify metastases earlier in patients who will not be cured.

Site of Primary

For patients presenting without recognizable metastases, the site of the primary tumor is thought to be of prognostic importance. Table 1 is taken from the excellent review paper of Lockshin and Higgins (11). This table shows 5-year survival figures from five reports of large series of osteosarcoma exclusive of Paget's sarcoma. The data suggest that patients with extremity primaries do better than those with primaries in the axial skeleton, clavicle, or scapula. Garrington et al (12) and Kragh et al (13) report that facial and jaw tumors do not have as poor a prognosis as do other axial skeletal tumors. These tumors often kill by local invasion rather than by metastasis after a considerable duration from onset. While the cure rate may be very low for these tumors, the 5-year survival can be > 30%. The table also indicates that patients with primaries in the tibia do better than those with primaries in the femur. Most studies have concluded that the more distal the primary, the better the prognosis, though often the number of cases limits the exact extent to which this can be evaluated. The surgical accessibility of the primary tumor is the most frequently given explanation for the effect of site on prognosis. Most large series report approximately one half of tumors arising in the femur and between one sixth and one fourth arising in the tibia or fibula (11). Table 2 shows a more detailed breakdown of primary sites taken from Dahlin and Coventry (6). Eighty percent of the femur tumors occurred in the lower portion of the bone and 78% of the tibia tumors occurred in the upper portion. Only 26% of their osteoid-producing primaries occurred below the elbow or knee. Of the primaries in long bones, only 31% were below the elbow or knee. Patients with primaries below the elbow or knee had a 5-year survival rate of 35.5%.

Duration of Symptoms

Two clinical characteristics studied have been proposed as indirect measures of tumor growth rate. The first is the time interval between the onset of symptoms and presentation for treatment. This time interval may be the result of several causes unrelated to growth rate, and its measurement is subjective. Some investigators deny that the duration of symptoms has any effect on prognosis, but in the large series of osteosarcoma patients reported by McKenna et al (8), the duration of symptoms in the 5-year survivors was twice as long as for those who did not survive for 5 years.

TABLE 1.—% 5-yr survival in osteosarcoma by site of primary tumor*

Authors (ref No.)	% 5-yr survival for osteosarcoma in—			
	Femur	Tibia	Total extremities	Axial skeleton, clavicle, scapula
Coley and Pool (15)	21	37	34	9
Dahlin and Coventry (6)	19	37	23	6
McKenna et al (8)	12	4	11	13
Price (16)	16	32	28	5
Weinfeld and Dudley (17)	16	31	15	6

**From* ref 11.

TABLE 2.—Primary site distribution in osteosarcoma*

Site	No. of patients treated before 1960
Sites readily treated surgically	
Hands and feet	3
Fibula	16
Tibia, lower and middle	19
Tibia, upper	63
Femur, lower	148
Femur, middle	21
Radius and ulna	6
Humerus, lower and middle	6
Subtotal	282
Sites difficult to treat	
Femur, upper	19
Humerus, upper	31
Scapula	7
Clavicle	2
Ilium	29
Ischium and pubis	8
Ribs	10
Sternum	1
Vertebra and sacrum	9
Skull	11
Subtotal	127
Total	409

**From* ref 6.

They also found this result for the parosteal patients, but not for patients with chondrosarcomas or fibrosarcomas. Ninety percent of the therapeutic failures were treated within 6 months of initial symptoms, whereas 50% of the cures were not treated until a longer interval had elapsed. Though the importance of the duration from symptoms until treatment is not definitively established, it seems reasonable that a rapidly growing tumor produces disturbing symptoms or metastases earlier than a slower growing one. The duration of the symptomatic period can be a very important parameter in comparing the results of recent to older studies. Most of the large series reported before the past few years are based on the treatment of patients who were seen at major research institutions due to established and relatively stable referral patterns. The prognosis of patients with osteosarcoma has been bleak and stable through most of the past several decades without promising new treatments being developed. When a promising new treatment is tried, referral patterns change and research institutions may accrue patients much more rapidly than before. Patients who have slower growing tumors and who stay free of detectable metastases long enough to travel to more distant locations and undergo thorough metastatic workups may tend to form a greater proportion of the study group than they would have in earlier series. This is particularly true if one accepts a patient as part of the study even though the surgery may have been performed in an outside institution. This may definitely bias the results, and it was for this reason that such patients were not included in the results of Dahlin and Coventry (6). When one recognizes how rapidly following surgery patients may develop pulmonary metastases (for example, one third of the 145 patients reported by Marcove et al [7] had developed pulmonary metastases within 6 months of surgery), one should be awed by the potential bias introduced by changing referral patterns.

Tumor Size

Size of the primary tumor at presentation is the second factor which has been proposed as a reflection of growth rate to influence prognosis. Table 3 is taken from the series of McKenna et al (8) of 417 patients treated by ablative surgery with curative intent. They concluded that the relation of tumor size to prognosis is direct, the smaller the tumor the better the survival rate, with the most striking effects seen for osteosarcomas and fibrosarcomas where there were no cures when the greatest dimension of the tumor exceeded 15 cm. Table 4 shows the distribution of tumor size for all of the patients in McKenna's series who were treated with surgery. There have been smaller studies that have not found such a striking relationship between tumor size and prognosis, and there is no indication of whether the size effect, if it is real, exists only through a correlation with tumor site.

Other Factors

Much of the literature addressing the influence of age on prognosis is confused by the pooling of subgroups known to have different prognoses and even different age distributions. It is impossible to adequately evaluate the effect of age if one includes cases of chondrosarcoma, fibrosarcoma, sarcoma

TABLE 3.—Relation of tumor size to 5-yr disease-free survival for patients treated with curative intent*

Tumor size (cm)	% 5-yr survival in—			
	Osteosarcoma	Chondrosarcoma	Fibrosarcoma	Parosteal osteogenic sarcoma
0–5	40	60	50	0/1
5–10	17	35	31	71
10–15	4	22	9	86
> 15	0	27	0	80
All sizes	14.4	29.1	22.6	76

**From* ref 8.

TABLE 4.—Distribution of tumor size for patients treated with surgery*

Tumor size (cm)	%			
	Osteo-sarcoma	Chondro-sarcoma	Fibro-sarcoma	Parosteal osteogenic sarcoma
0–5	6	6	8	5
6–10	58	54	58	35
11–15	27	27	22	35
> 15	9	13	12	25

*From ref 8.

arising in a site of Paget's disease, or sarcomas of the face and the jaws, because all of these subgroups tend to occur later in life than does osteosarcoma. Marcove et al (7) avoided these difficulties in their report of 145 cases of osteosarcoma in patients < 21 years old. They found that patients in the second decade of life had a median survival of 9 months compared to 5 months for patients in the first decade of life. This difference was statistically significant though the cure rates were no different.

In discussing age, it should be mentioned that cases of osteosarcoma arising in a site of Paget's disease should always be evaluated separately. Paget's disease and Paget's sarcoma are most prominent in the age range of 50–70 years. In McKenna's (14) series of 33 patients with osteogenic sarcoma (in his broader sense) in a site of Paget's disease, only one patient was < 40 years old. None of the patients survived for > 5 years, only four lived for > 24 months, and the median survival time was 7 months. An age-matched control group of osteogenic sarcoma patients without Paget's disease had a 5-year survival rate of 14%, and a median survival of 17 months. The Paget and control group differed in histology and anatomic distribution of tumor, but one can conclude that although there are reported cases of 5-year survivals in osteosarcoma patients with Paget's disease, the prognosis is especially bleak.

Several other clinical features such as sex, the presence of pathologic fractures, radiologic appearance, or serum alkaline phosphatase do not appear to be of significant prognostic importance, though in some cases this cannot be concluded with great reliability.

DISCUSSION

Osteogenic sarcoma is sometimes thought of as a homogeneous or predictable disease, but this is not the case. By selecting patients based upon pathologic and clinical prognostic factors, one could obtain satisfying survival statistics. Nevertheless, when one examines reports of large series of cases of osteosarcoma at different institutions or at the same institution for different time periods in which the pathologic diagnosis has been carefully reviewed, one usually finds relatively constant 15%–30% 5-year survival rates. This result is often misinterpreted to mean that the 15%–30% rates can be expected in all situations unless the treatment improves. Large series of patients accumulated over relatively long periods of time with stable referral patterns produce survival statistics that are representative of a certain difficult-to-define subpopulation of patients. Large institutions in different parts of the country may be studying essentially the same subpopulation. This does not mean that we can expect these survival figures to apply to small samples of patients accrued with a different referral pattern. The prognosis of a patient is not a random phenomenon selected from a statistical distribution. Prognosis is determined by biologic parameters and treatment. In comparing the results of two studies, we must thoroughly evaluate the extent to which the patients are comparable with regard to known prognostic factors. To the extent that important prognostic factors are unknown to us, our comparisons are not formed on a sound basis. We may be very wrong in assuming that the values of unknown prognostic factors can be viewed as a random selection from a statistical distribution appropriate to others or other times. The relative constancy of survival rates over time and at other institutions may have no relevance in ensuring that we are not inadvertently selecting a relatively favorable population of patients for our encouraging studies.

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Osteogenic Sarcoma Treatment Overview and Some Comments on Interpretation of Clinical Trial Data

Stephen K. Carter* and Michael Friedman[1]

Malignant bone and cartilage tumors constitute < 1% of all malignant neoplasms (1). They occur most commonly in the pediatric age group and account for a mortality of 1.87/million children < 14 years old. The incidence rises for slightly older patients, in whom these tumors are responsible for 11.97 deaths/million people between 15 and 19 years old (2). This relatively low incidence belies the significance both emotionally, in that it affects mostly children and young adults with a mortality rate that comes close to the incidence rate especially with osteosarcoma, and socially, by its impact on work years lost compared to more prevalent cancers (3).

Osteogenic sarcoma is the most frequently diagnosed malignant primary tumor of the bone. The peak incidence is between 10 and 25 years. It is observed in males more commonly than in females, with the ratio being 1.6–2 to 1 (4). The tumor location most often observed is in the diaphysis, especially of the lower extremity (5). Approximately one half of the tumors affect the femur, with 80% of these arising in the distal end. Other sites of origin are, in rough order of incidence: proximal femur, proximal humerus, tibia, pelvis, jaw, and phalanges.

An initial obstacle to controlling osteosarcoma is the inability to make an early diagnosis. The only consistent symptom is bone pain which usually starts as a vague complaint that does not make parents or physicians think of a tumor. The average patient with osteosarcoma is first seen by a physician after 3 months of symptoms (6). Systemic symptoms other than pain are uncommon. A second major obstacle to the effective control of osteosarcoma is the lack of any collaborative laboratory study. Most blood studies are not useful. Serum alkaline phosphatase is often elevated, but it is elevated in numerous other conditions where osteoid is produced.

The major initial diagnostic procedure is the radiographic examination. If there is suspicion of tumor, then an open biopsy is performed with a tourniquet applied to the limb above the tumor. When the results of all investigations are completed, it is common at some centers (4) to call an interdisciplinary conference with participation of the radiologist, radiotherapist, pathologist, orthopedic surgeon, general surgeon, pediatric medical oncologist, social worker, and psychiatrist concerning the decision of which therapy to use.

The major therapeutic approach to osteosarcoma has been, for many years, radical surgery. Surgical resection is planned with the objective of achieving complete tumor ablation. The site of amputation is dependent on the location of the primary tumor. The affected bone is sectioned at least 3 inches above the proximal limit of the intramedullary extent of tumor visible roentgenographically. If the tibia or fibula is the involved bone, an above-the-knee amputation or disarticulation through the knee joint may be performed. Lesions of the foot require a below-the-knee amputation. A hemipelvectomy may be performed for tumors of the innominate bone and a forequarter amputation for lesions of the upper humerus.

In most centers the patient is fitted with a prosthesis immediately after lower limb surgery. It consists of a rigid dressing pylon and a foot-ankle assembly. The intermediate prosthesis permits early ambulation and improves the psychologic outlook. A definitive prosthesis can usually be fitted 6–8 weeks later.

Friedman and Carter (7) have reviewed the surgical results from the literature compiling data on some 1337 patients. Despite differences in pretherapeutic workup, surgical techniques, and demography, there has been a striking consistency (> 25 years of investigation) in 5-year survival rates. The overall 5-year survival rate in this review was 19.7% (253 of 1286 patients). The range was fairly small, 16%–23%, in the series reviewed. Of 438 patients with 10-year followup the survival rate was 16% suggesting that the majority of patients who are living for 5 years apparently free of disease are in fact "cured."

These results are often used as historical controls for ongoing clinical investigations of new combined-modality therapeutic attempts. The rationale for

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TABLE 1.—Median survival using 3 treatment approaches (*from* ref 11)

Interval (mos)	% of patients surviving		
	Radiotherapy (total, 51 patients)	Amputation (total, 61 patients)	Both (total, 80 patients)
0	100	100	100
6	82	87	90
12	51	57	64
24	20	38	40
36	16	25	34
48	12	23	29
60	12	23	28
	Median survival (mos)		
	12.4	16.5	18.9

this has been that (*a*) the surgery-alone results have been consistent; (*b*) the prognosis with surgery only is poor; and (*c*) the numbers of patients available for study are generally small. The risk that is involved in this approach is that the current results with surgery may be superior to the often quoted 20% disease-free survival. The reason for this is the development of more rigorous pretreatment workups to rule out small but clinically detectable metastatic disease. Not many of the earlier series quoted by Friedman and Carter utilized techniques such as bone scanning and full-lung tomography. If, in addition, new small therapeutic series include patients with intrinsically better histopathology (parosteal lesions, chondrosarcomas, etc) the difficulty in interpretation of some of the new improved results becomes evident.

The data for radiation therapy, either alone or with surgery, are not as extensive as for surgery alone but are significant. In 143 evaluable patients reviewed by Friedman and Carter (7), treated with a variety of sources and a variety of total doses on several schedules, the overall 5-year survival rate was 12.5% (18 of 143 patients). It is difficult to evaluate the comparability of this response rate to traditional surgery, since:

a. Some patients could have had metastatic disease at presentation and therefore were ineligible for surgery.
b. Some had primary unresectable disease (skull, spine, or rib).
c. Some may have had significant medical illnesses mitigating against surgery.
d. True tumoricidal dosage was not utilized in all the patients (6000–12,000 rads total) (8).

However, there can be no doubt that radiation therapy in higher doses is capable of effecting some 5-year disease-free survivals.

In an attempt to select those patients who would respond more favorably, radiation therapy has been given prior to surgical ablation. This was based on the observations of Ferguson (9) and others (10) who found that those patients who survived metastasis-free for several months after definitive diagnosis had a better prognosis. A number of investigators used preoperative primary-site radiation to sterilize any tumor microemboli which would be released in surgery. The proposition was that fatal metastatic consequences resulted from surgical perturbation and spread of the tumor. Eight such studies which used a variety of doses, schedules, and intervals to surgery totalling 396 patients have been reviewed with 73 patients as 5-year survivors (19.8%). This is very similar to the results of the surgery-alone series. At this point, no convincing argument can be made supporting radiation over surgery alone in terms of long-term survival.

The median survival of patients treated with the three primary approaches to therapy has been documented by Sweetnam et al (11) (table 1). A definitive point in therapy is the appearance of recognizable pulmonary metastases. Sweetnam et al (11) noted that for any treatment regimen (surgery, radiation, or both), the median time to metastatic disease was 10 months. Francis et al (12) have noted a similar time period (11.1 months) to recurrence in a group treated with radiation and surgery. More significantly, Sweetnam et al (11) have demonstrated that the average time between recognition of pulmonary disease and death was 6 months.

Osteogenic sarcoma is associated with a variety of features that affect the prognosis (13). This tumor can arise in a focus of Paget's disease (frequently in older patients), often affecting not long bones (as in the younger group) but the axial skeleton (pelvis, skull, vertebrae, etc). This disease has a much

poorer prognosis and there are very infrequent 5-year survivors (5,10,14). In contrast, parosteal (or juxtacortical) forms of osteogenic sarcoma have a lower malignant potential and superior resectability. This is reflected in a 5-year survival of about 50% (1,15,16). More rarely, osteogenic sarcoma may involve a bone previously irradiated or may arise in an abnormal bone or (quite rarely now) be associated with industrial radium ingestion. The clinical course of these infrequent forms does not appear to differ significantly from the more common variety (17–19).

Many investigators have attempted to assess the relationship between degree of histologic malignancy and prognosis. Using Broder's criteria for grading, there has been varying enthusiasm among investigators. Most osteogenic sarcomas are of the higher grades (III and IV) and these dominate the clinical material in most series. Although the grade I and II tumors may have a better prognosis, they are too infrequent to significantly affect pretherapeutic stratification for randomization purposes (5). Price has employed a technique of grading according to mitotic frequency, which gives similar information (20–22).

A variety of other histopathologic techniques, such as elastic tissue staining to denote vascular invasion, have not been widely applied.

Specific Surgical Considerations

The size and location of the primary tumor correlate with resectability and curability. McKenna et al (10) have demonstrated that patients with tumors > 10 cm in size stand a sevenfold smaller chance of surviving 5 years than do patients with tumors of smaller size. In general, those tumors more distal to the axial skeleton (with the exception of facio-maxillary primaries [23,24]) can be more aggressively attacked and with better results (5,22,25,26).

The period of symptom duration leading to definite diagnosis and therapy is equivocally related to prognosis. In retrospective fashion, McKenna et al (10) and Cederlof et al (27) found that patients with a longer symptomatic course did better than those patients presenting after a shorter interval (7.3 vs 3.7 months). In McKenna's series, 90% of the therapeutic failures were treated within 6 months of initial symptoms, whereas 55% of the cures were not treated until a longer elapsed interval (10). However, Tudway could identify no such difference (3.7 vs 3.8 months) (28). In general, most series report a 2.5–< 10 months' duration of symptoms.

Clearly, earlier diagnosis and symptoms may reflect a more malignant course, whereas a lingering indolent prodrome may suggest host immunity or other factors at work.

Evaluation of the tumor doubling times (as judged by serial measurements of chest lesions) has been employed to judge the tempo of disease progression. Morton has used this measurement to evaluate candidates for resection of discrete (few) pulmonary lesions.

No unequivocal correlation to survival has been described for many other factors. The sex of the patient has not been a critical determinant in most reported series (5). Foster and Shambaugh suggest a better prognosis for females (29), while others have noted a similar, but statistically insignificant, trend (12,25). Similarly, the age of the patients is not critical, except that the proportion of tumors arising in foci of Paget's disease increases after age 60. This small group of patients does very poorly. The presence of pathologic fractures (23), radiologic appearance (30), etc, has not yielded significant data.

Pathologic Data

At least two large studies have described their series of autopsied patients. In Phelan and Cabrera's series of 50 patients there were 12 autopsies; six of 12 had lymph node metastases, two of 12 had myocardial disease, and blood vessel invasion and vascular emboli were seen frequently (31). McKenna describes initial (at symptomatic presentation) involvement of lung in 10% and bone in 3%. At autopsy the distribution of organ involvement was as follows:

Lung	95%
Local recurrence	50%
Nodes	31%
Pleura	30%
Pericardium	18%
Kidney	12%
Liver, pancreas, dura	8%
Adrenal	6%
Thyroid	4%
Ovary	2%

Vascular invasion was noted in 14% and inferior vena cava obstruction in 8% (23).

Chemotherapy Studies

The most exciting development in the therapy for osteogenic sarcoma has been the evolution of the use of chemotherapy as an adjunct to primary local ablative therapy. The theoretic assumptions which have been utilized in developing this strategy are as follows:

a. Osteosarcoma is microscopically disseminated

at the time of diagnosis in most cases as evidenced by the rapid and frequent development of pulmonary metastasis soon after amputation.

b. Chemotherapy is more effective against minimal residual disease than against relatively large tumors.

c. Drugs now exist which can shrink clinically evident metastatic disease.

d. These drugs, when utilized immediately after local ablative therapy has removed the bulk of the tumor cells, will eradicate the remaining microscopic foci.

e. In order to achieve control or "cure," all malignant cells have to be destroyed, removed, or neutralized.

This approach is now being widely utilized in solid tumor treatment (32).

In the 1960s, chemotherapy was utilized to treat metastatic osteosarcoma with generally poor results. Drugs such as cyclophosphamide, melphalan, mitomycin C, actinomycin D, and vincristine produced occasional regressions but were not considered meaningfully active (7,33). In the 1970s, two active regimens were uncovered for metastatic disease which caused optimism to develop about the combined-modality approach.

The first approach involved an old drug, methotrexate, given in massive doses in combination with citrovorum factor rescue. The rationale for this approach is that citrovorum factor is a reduced folate that bypasses the biochemical block caused by methotrexate. Thus, citrovorum factor rescue allows the use of very large doses of methotrexate which produces high drug concentrations in tumor cells while the systemic toxicity is prevented. In 1954 Goldin et al (34) showed this experimentally and Djerassi et al (35) first reported on it clinically. Jaffe et al were the first to show the effect of this approach on metastatic osteosarcoma (36). They reported a 40% response rate (four of ten patients) with this combination.

The second approach involves a relatively new antitumor antibiotic, adriamycin, originally developed in Italy by the Farmitalia Company, which has been proven to be active against a wide range of human malignancy (37). Cortes et al (38) reported objective responses in seven of 17 patients with advanced disease and Gottlieb et al (39) reported responses in eight of 18 patients when adriamycin was combined with another drug, DTIC. Combinations involving the drugs with activity have been reported by Wilbur et al (40), Sutow et al (41), and Rosen et al (42).

As a result of these studies, a wide range of trials were initiated in which chemotherapy was given immediately after surgery, and preliminary reports of prolonged disease-free interval and survival appeared in the scientific literature and the lay press.

At the Sidney Farber Cancer Institute (43), 22 consecutive patients with osteosarcoma received adjunctive chemotherapy beginning 3 weeks after local treatment of the primary tumor with operation or radiation. The chemotherapy given consisted of vincristine, 2 mg/m² iv, followed in 30 minutes by methotrexate given by continuous infusion over a 6-hour period. The initial dose was 1500 mg/m². The treatment was given at 2-week intervals with dose escalations to a maximum of 7600 mg/m². Subsequent to this study, the importance of adequate hydration, alkalinization of the urine, and monitoring of the serum methotrexate levels have been shown to be of great importance if significant drug-related mortality is to be avoided. It has also become clear that this is a therapeutic approach which should only be undertaken by a center with adequate resources of experienced personnel and support services.

In comparison to a historical control group from the same institution in which 78% of patients developed pulmonary metastasis at 12 months, only two of 20 study patients were found to have recurrence at the time of the initial report. Further followup at a later date revealed that 52% of study patients were free of disease 2 years after therapy (Jaffe N, personal communication). In the initial study only 15 of 20 patients had "classic" osteogenic sarcoma with four having parosteal osteogenic sarcoma and one multifocal sclerosing osteogenic sarcoma. Three of the 15 patients with the classic osteogenic sarcoma in the study group had chondrosarcoma elements in their tumor which might be classified as osteochondrosarcoma. Of the 15 patients with classic osteogenic sarcoma, only 12 had definitive local treatment in which local control was achieved. Eight of these had amputation only, and four received radiotherapy followed in 3–5 months by amputation. The results are compared to a historical control group of 78 patients with local control treated between 1950 and 1972. These two groups were comparable as to age distribution and sex, but are not matched for any other prognostic variables such as methodology of local control, histology, tumor location, tumor size, or pretreatment workup, for evidence of metastatic disease.

Cortes et al (44), reporting for the Acute Leukemia Group B, described 21 patients who were given adriamycin, 30 mg/m²/day × 3 every 4–6 weeks for six courses beginning 2 weeks (median) after surgical amputation of the primary lesion. Four patients however were treated > 8 weeks after amputation. The data of Marcove et al (45) were utilized as a

historical control. Five of the 21 study patients had relapsed at the time of the initial report (subsequent reports show about half of the patients free of disease at 2 years) (Cortes E, personal communication). Of the 21 study patients, only 15 had radical amputation. Of the six patients who had "subradical" amputation, four had recurrence at the time of the report.

The Pediatric Division of the Southwest Oncology Group has a long history of adjuvant chemotherapy treatment of osteogenic sarcoma beginning in 1963 as reported by Sutow et al (41). This first study involved 14 consecutive patients treated with melphalan with only two achieving long-term survival. Beginning in 1968, a group of 11 children with nonmetastatic osteogenic sarcoma were treated with a three-drug pulse regimen of vincristine, actinomycin D, and cyclophosphamide. Of these 11 patients, three (27%) are long-term survivors. In 1971, a study was undertaken of a four-drug adjuvant regimen called CONPADRI-I (cyclophosphamide, vincristine [Oncovin], melphalan [phenylalanine mustard], and adriamycin). Chemotherapy was instituted as soon as satisfactory wound healing was observed. Eighteen patients were treated with this regimen and at present, ten (55%) remain disease-free for prolonged periods (Sutow WW, personal communication). Subsequent studies (COMPADRI-II and COMPADRI-III) have attempted to add high-dose methotrexate to the initial four-drug regimen.

The studies described above, plus those being performed at St. Jude Children's Research Hospital, Children's Hospital at Stanford, and the Memorial Sloan-Kettering Cancer Center, have all reported disease-free and survival rates superior to those of historical control series but all involve small numbers of patients with minimal matching of prognostic variables. The interpretation of adjuvant studies is clouded by the fact that historical controls were used and the possibility exists that more stringent diagnostic criteria for exclusion of metastases and more careful case selection may have been used in the newer studies in comparison to the large retrospective analysis used for historical control purposes. There are data from the Mayo Clinic indicating that the 2-year disease-free interval in the kind of cases currently selected for adjuvant trials may be twice that reported in the series of Marcove and others utilized as historical controls. Preliminary reports of adjuvant activity for materials such as interferon, transfer factors, and anticoagulation make one uneasy that, with more careful case selection combined with early data analysis, almost anything can be seen to be positive when compared to the earlier data base. We need a more careful delineation of the critical factors known to affect survival, eg, histology, size of lesion, surgical procedure, location of lesion, etc, in the current series as compared to older series before we can feel absolutely confident about the correlations we would like to make in this disease.

DISCUSSION

Osteosarcoma is a tumor in which adjuvant chemotherapy is considered by many to be a clear-cut success. The data supporting this come from a series of clinical trials which all share certain characteristics. These are small numbers of patients in the treatment series with results compared to a retrospective historical control. This is supported by the arguments that osteosarcoma is a relatively rare tumor and that prior results reported with amputation, radiation, or the combination of both were consistently dismal, with the cure rate hovering about the 15%–20% range. The assumptions inherent in these studies are that there are not systematic differences between the old series and the treated series due to changing referral patterns in the study center, changes in supportive therapy, changes in the skill of the doctors, or subconscious (or even conscious) selective biases. Unfortunately, all of the reported series make little if any attempt to compare the treated group with their historical controls to prove that their assumptions of comparability are valid. This is so important in osteosarcoma trials because the numbers of patients in the treated series are so small.

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Surgical Treatment of Osteogenic Sarcoma at the Mayo Clinic

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SUMMARY

Osteogenic sarcoma continues to present a tremendous therapeutic challenge. Until recently, treatment has continued at a relatively unsophisticated level. Although amputation, usually at a cross-bone level with a safe margin above the lesion, continues to be the treatment of choice, increased interest is being demonstrated in radical en bloc limb-saving resections. Modern joint implants are proving effective in restoring the osseous integrity and joint function after the resection.

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The management of bone tumors presents many therapeutic problems, and certainly the most challenging area of orthopedic oncology lies in the management of osteogenic sarcoma. In 1969, the Section of Orthopedic Oncology was developed at the Mayo Clinic to meet the challenge of this dread disease. At present, the management of all patients with osteogenic sarcoma is under the direction of an osteogenic sarcoma study group, which is a multidisciplinary group. In addition, research activities in our orthopedic oncology laboratory include, among other things, pretreatment and posttreatment immunologic surveillance of all osteogenic sarcoma patients. To date, approximately 1000 patients with osteogenic sarcoma have been seen and treated at the Mayo Clinic.

After careful preoperative assessment to determine the extent of local involvement of the tumor and to detect any evidence of systemic occult metastatic disease, treatment is undertaken. The primary tumor confronts the surgeon with the problem not only of eradicating the tumor but also of restoring function in the extremity. In osteogenic sarcoma, the chief aim is to save the patient's life, and inadequate cancer surgery aimed at saving the limb may jeopardize the life of the patient. We must give each patient the maximum benefit of surgical treatment as it applies to his individual case. Although the treatment may be individualized according to the various subvarieties of osteogenic sarcoma, this presentation outlines more specifically our approach to the usual high-grade central osteogenic sarcoma (1,2).

Biopsy

Treatment depends on an accurate histologic diagnosis, and for this reason, we believe that adequate tissue samples should be obtained by a wisely placed, carefully planned open biopsy. We believe that the biopsy is preferably done when definitive therapy can be carried out at the same time, and we make a plea for biopsy and definitive treatment at the same surgical exposure to avoid delay between the time of biopsy and surgery. Sending slides of biopsy tissue to several pathologists for an opinion may create an unnecessary delay. Part of the tumor will contain soft tissue which can be prepared by a rapid frozen-section technique and interpreted by the pathologist (3). Definitive treatment can then be carried out. This plan presupposes that there is first, a pathologist who is well versed in the histologic appearance of malignant tumors of bone; second, a laboratory equipped to do rapid frozen section; and third, an orthopedic surgeon who has complete confidence in the pathologist's interpretation and in his own judgment and who can go ahead with definitive therapy after the diagnosis has been made. It is our belief that patients with suspected malignant bone tumors should be referred to centers where such a plan of treatment is available.

Regarding the specific surgical technique, the limb is first surgically prepared with care so as not to cause mechanical disturbance of the tumor and

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thereby force additional malignant cells into the circulation (4). Previously, we utilized a sterile rubber tourniquet placed proximal to the tumor in an effort to avoid further dissemination of tumor cells into the bloodstream during the biopsy. However, there has been no evidence to suggest that this technique has been effective (2), and it has not been used at the Mayo Clinic in recent years. In addition to altering the dynamics of the intraosseous circulation and possibly compressing an ill-defined soft tissue tumor mass by such a maneuver, along with the demonstration of the constancy of circulating tumor cells, recent work suggests the role of fibrin clots in the implanting of metastatic deposits, and certainly the congestion distal to a tourniquet would potentiate this phenomenon.

Surgical Treatment

Amputation

At present, amputation remains the treatment of choice in osteogenic sarcoma. Statistical evidence supports amputation as the best method of treatment for these tumors under usual circumstances (4). Although it is difficult for us to do an amputation because of the mutilation and obviously deforming results, less radical measures are usually inadequate for these radioresistant tumors. On the other hand, a living person without one of his limbs can be a happy person and a useful member of society.

At what level should the amputation be done? The point is to eradicate the tumor completely, and the surgeon's second responsibility is to preserve as much function as possible. Our experience indicates no added safety in leaving a joint between the tumor and the site of amputation, and we have traditionally done cross-bone amputation for low femoral lesions (fig 1). However, we would emphasize that these are high amputations at the junction of the proximal and middle thirds of the femur, and this leaves a fairly wide safety zone, bearing in mind the factor of medullary extension. We continue to perform these amputations at the high thigh level because of the better functional restoration and better quality of life that this operation affords the amputee, and because of the confidence we have in our surgical pathologists in doing fresh-frozen examinations of the proximal marrow at the time of surgery. In a recent critical analysis of 100 patients seen in the 1960s and early 1970s, we have documented only two femoral stump recurrences.[2] Watts[3] and Eilber[4] similarly report a low incidence of local recurrence after cross-bone amputation. We are certainly familiar with the excellent work by Enneking and Kagan (5) on skip lesions in osteogenic sarcoma, and stump recurrence may become a bigger problem if these patients live longer under the influence of adjunctive chemotherapy.

Radical En Bloc Resection

A limb-saving radical en bloc resection of an osteogenic sarcoma may be a valid alternative to amputation in carefully selected instances. Previously, even if the first goal of segmental resection of the lesions could be achieved, the means available to restore the integrity of bone and joint function in the resected area were inadequate, and therefore little interest was shown in this form of treatment despite its limb-saving potential. However, with possible recent advances in adjunctive treatment (6–9), coupled with improvements in oncologic surgery and techniques of reconstruction (10,11), radical en bloc resection of these lesions has been given greater consideration.

Various factors must be considered (11–13). Reconstructive techniques after resection are generally applicable to older patients whose epiphyses have closed. For those children who are still growing, we believe that amputation probably is the only realistic surgical procedure at this time. In addition, the location and extent of the tumor must be favorable to permit removal with a sufficient margin to prevent local recurrence, but not so extensive as to preclude restoration of useful function. The tumor should be totally intraosseous or have a very small soft tissue extension without involvement of major neurovascular structures. It should involve only a reasonably short segment of the affected bone. The simplest application of total resection without amputation may be used when the lesion is located in a totally or partially expendable bone that does not need replacement, such as the scapula, the clavicle, a single forearm bone, the innominate bone, or the fibula. In these primary tumor locations, the size and extent of the soft tissue component will determine whether or not a limb-saving operation can be done.

Between the years 1963 and 1974, 181 patients with the classic type of primary localized osteogenic sarcoma had their initial treatment at the Mayo Clinic. During this time, 11 patients were treated primarily with radical en bloc resection of the

[2]Pritchard DJ, Ivins JC, Sim FH, et al. Unpublished data.

[3]Watts H. The surgical treatment of osteosarcoma. Presented at the meeting of the Osteogenic Study Group, National Cancer Institute, Bethesda, Md, Jan 19, 1977.

[4]Eilber F. Personal communication.

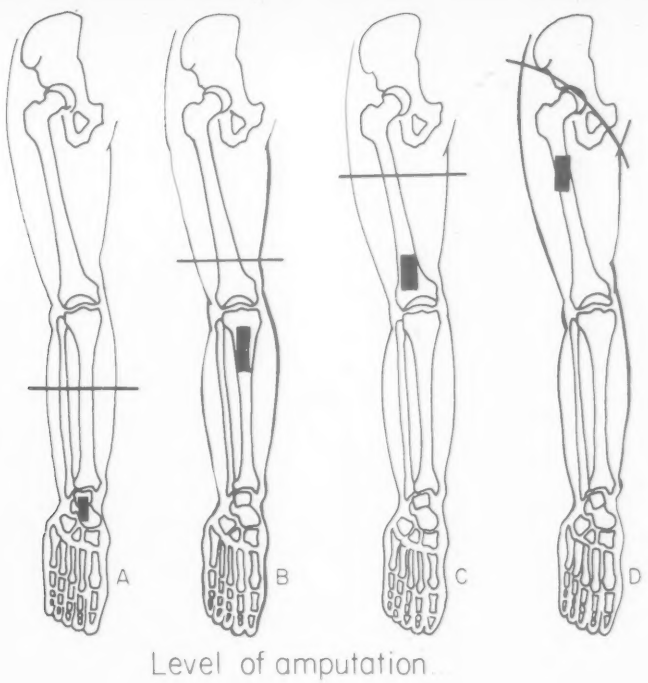

FIGURE 1.—Level of amputation for osteogenic sarcoma of lower extremity.

osteogenic sarcoma. Since 1974, four additional patients have been treated with resection. Of these 15 patients, ten were female and five were male and they ranged in age from 13 to 65 years (average, 21.5 years). Overall, ten patients remain alive after 3 months to 10 years of followup and five have died with metastatic disease. Two of the patients who died had evidence of local recurrence of the sarcoma. However, one cannot compare the results of this treatment with those in patients who underwent amputation during this period because the patients who had radical resection were generally carefully selected.

Of the 15 patients who underwent en bloc resection for cure, six had lesions involving the proximal femur. Two of these six remained free of disease after 6 and 7 years, and two others died within 1 year. The remaining two died of their disease during the second year; of these, one had a hip disarticulation for local recurrence 4 months after operation but died with metastatic disease 22 months after onset of the disease. Two patients remained alive and well 3 and 6 months after resection of the distal femur and segmental total-knee arthroplasty. Two patients had resection of lesions of the proximal fibula, and they have no evidence of disease 1 and 8 years postoperatively. Two patients remained free of disease 3 and 10 years after scapulectomy. One of two patients undergoing pelvic resection for osteosarcoma died 4 months later with evidence of local recurrence and metastatic spread, and the other is free of disease 7 years later. The other patient had resection of an osteosarcoma of the distal ulna and has no evidence of disease 3 years later.

Among the patients who were treated with radical en bloc resection, five had radiation therapy, two of them preoperatively. Three of these patients also had adjuvant chemotherapy. In addition, two patients had adjuvant chemotherapy alone.

A preliminary report by Rosen et al (10) indicated that preoperative chemotherapy was effective in reducing the size of the primary osteosarcoma and making the tumor locally resectable. They reported no evidence of local recurrence 2–15 months postoperatively in 15 patients who were treated by aggressive preoperative chemotherapy followed by en bloc resection and prosthetic replacement. After surgery, aggressive chemotherapy was continued for 1 year.

Reconstruction

As techniques of oncologic resection become more refined, particularly if chemotherapy proves to have a tumoricidal effect—shrinking the size of the tumor and making osteogenic sarcoma more resectable (10)—we must obviously continue to improve our specialized techniques of oncologic reconstruction. The methods of restoration of skeletal integrity after radical resection of an osseous lesion will vary according to the location of the tumor. Allograft replacement continues to have many enthusiasts (14,15), and with improvements in selection and typing, this biologic replacement method may gain more support. After resection of a lesion in the distal femur, particularly in young persons, a segmental arthrodesis is a single definitive procedure that provides a stable weight-bearing extremity. Various methods may be used to achieve the segmental arthrodesis. The method we prefer is to utilize a segmental hemicylindrical sliding graft from the ipsilateral tibia, as described by D'Aubigné and Dejouany (16). Another procedure that we have used in several instances is a cross-leg graft—that is, removing half of the amount of resected bone from the trochanteric area of the contralateral femur and inserting this into the defect. In this way, the patient is able to achieve consolidation of the bone grafts over a smaller distance and both legs remain of equal length. Another technique that holds a great deal of promise is use of a fiber-metal implant to restore the integrity of the resected bone, and we have recently reported five cases in which this technique was utilized (17). This has the advantage that the ipsilateral tibia is not compromised, nor is there any compromise of the contralateral femur in achieving the segmental replacement.

Application of recent advances in reconstructive orthopedic surgery to orthopedic oncology has been very rewarding, and use of modern joint implants has provided an effective means of restoring the osseous integrity and maintaining the physiologic function of the joint (10,11). To date, we have carried out a custom segmental prosthetic replacement of the proximal one third or the distal one third of the femur in 42 patients. The resection must follow the established principles of oncologic surgery, with removal of the tumor and a surrounding envelope of normal muscle and tissue. In the distal femur, this means removal of the surrounding muscle, capsule, and ligaments, with preservation of the rectus femoris for extension of the knee. Because of the loss of stabilizing capsule and ligaments, this method necessitates the use of a custom segmental hinged arthroplasty; our current design, consisting of a modified Waldius hinge, is shown in figure 2. At present, we have available custom special segmental total-knee replacement prostheses allowing replacement of 6.5–175 mm of bone, so that the resection and the reconstructive procedure can be carried out at the same surgical exposure. Similarly, the proximal femur lends itself to reconstruction with a segmental prosthetic total-hip arthroplasty after resection of the tumor. For this we have special segmental prosthetic implants varying from 80 to 170 mm in length (fig 3).

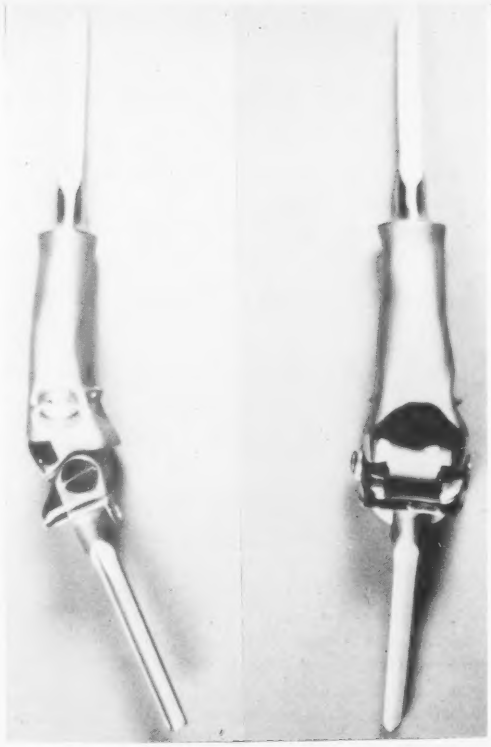

FIGURE 2.—Custom segmental replacement prosthesis of distal femur.

We recently reported 20 patients with tumors involving the hip and 18 patients with tumors in the knee region who were treated with resection and segmental prosthetic replacement.[6] The types of osseous lesions resected are shown in table 1. Twenty-seven patients had primary bone tumors, of which 17 were malignant. Five of these were osteogenic sarcomas. The followup ranges from 3 to 56 months (average, 13 months) for the proximal femur

[6]Sim FH, and Chao EYS. Segmental prosthetic replacement of the knee. Presented at the Annual Meeting of the American Orthopaedic Association, Boca Raton, Fla, June 27–30, 1977.

FIGURE 3.—Special segmental replacement prosthesis of proximal femur ranging from 80 to 170 mm.

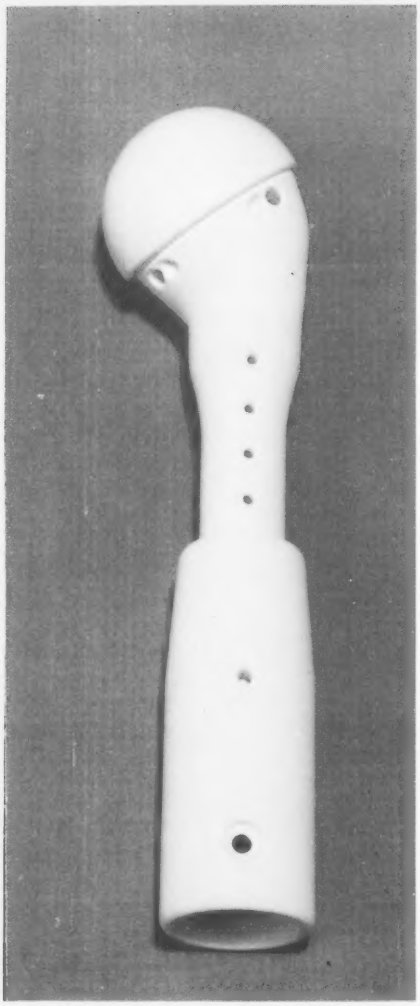

FIGURE 4.—Ceramic hemiarthroplasty replacement of proximal humerus.

TABLE 1.—Segmental replacement of proximal femur and knee: types of osseous lesions

Type of lesion	No. of patients
Proximal femur	
Primary neoplasms	
Osteogenic sarcoma	3
Chondrosarcoma	3
Fibrosarcoma	1
Reticulum cell sarcoma	1
Giant cell tumor	1
Myeloma	1
Total	10
Secondary neoplasms	
Hypernephroma	5
Breast	3
Lung	2
Total	10
Distal femur or proximal tibia	
Primary neoplasms	
Giant cell tumor	8
Chondrosarcoma	3
Osteogenic sarcoma	2
Fibrosarcoma	1
Ewing's sarcoma	1
Solitary myeloma	1
Chondroblastoma	1
Total	17

and from 2 to 26 months (average, 12.5 months) for the knee. This special reconstructive procedure was successful in providing excellent functional recovery of the joint after the resection. In the hip, 19 of the 20 patients had excellent relief of pain. All but one patient (with metastatic cancer) were able to ambulate independently. The range of knee motion achieved after segmental knee replacement was 0°–140° (average, 88°). In analyzing the results of the 14 knee patients followed for ≥ 6 months, only three patients had mild discomfort with increased activity. All but one patient were unlimited in their normal walking activity. Of the five patients who had resection and segmental replacement for osteogenic sarcoma, two have died with metastatic disease at 9 and 18 months. We have had no evidence of local recurrence in this group of patients.

In the proximal humerus, we previously used a custom Vitallium hemiarthroplasty with intramedullary fixation for reconstruction after resection of an osseous lesion. However, our present approach is to use a multicomponent ceramic hemiarthroplasty with a cone fixation that allows ingrowth of bone (fig 4). This method has definite advantages over the previous technique: methyl methacrylate is not needed for fixation and almost any size of defect can be reconstructed with this system, which consists of multiple interchangeable components.

The functional requirements of these special reconstructive procedures are demanding, and they provide a challenging problem biomechanically. For this reason, careful evaluation of these patients in our biomechanics laboratory is essential, with close liaison between surgeon and engineer regarding the

implant design, rehabilitation, and evaluation of the functional performance of the patient (18).[7]

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Adjuvant Therapy for Osteosarcoma: Preoperative and Postoperative Treatment [1]

Frederick R. Eilber,* Todd Grant, and Donald L. Morton [2]

SUMMARY

Seventeen consecutive patients with osteogenic sarcoma participated in a prospective study to ascertain first, whether postoperative adjuvant chemotherapy or chemoimmunotherapy could reduce the incidence of distant metastases and second, whether in situ tumor cell destruction could be achieved with preoperative chemotherapy and radiation therapy. To date 14 of 17 patients (85%) are alive and free of disease for a median survival time of 11 months. Three patients developed recurrent disease, one with local recurrence in the tibia and two with pulmonary metastases. Limb salvage was attained in 12 patients by cadaver allografts and in one patient by radiation alone at 6 months.

[Cancer Treat Rep 62:213–216, 1978]

With the advent of systemically active chemotherapeutic agents for the treatment of osteosarcoma, the potential for effective adjuvant treatment for patients with this disease became a reality (1–7). In July 1974, the UCLA Division of Surgical Oncology began a prospective study of patients with osteogenic sarcoma with two primary goals. Our first effort was directed to an evaluation of postoperative adjuvant chemotherapy with adriamycin and high-dose methotrexate to determine whether distant metastatic disease could be prevented to prolong life. Because these agents had been shown to be highly effective and because of a well-documented natural history of the disease (8–10), there was no concomitant treated control group included in the study. Instead, patients were randomized between chemotherapy alone and chemoimmunotherapy in order to assess the potential value of immunotherapy for this disease (11). Our second major goal was to determine whether it was possible to effect in situ tumor destruction by preoperative treatment of these tumors with intra-arterial adriamycin (12,13) and radiation therapy (14) before radical en bloc excision of involved bone or soft tissue to allow preservation of the involved extremity.

PATIENTS AND METHODS

From July 1974 to November 1976, 17 consecutive patients with osteogenic sarcoma were evaluated by the Division of Surgical Oncology, UCLA School of Medicine. The age range for these patients was from 5 to 32 years, with a median of 16 years. There were six females and 11 males. Primary tumors were located as follows. Of nine patients who had lesions of the femur, seven were distal, one was midfemoral, and one was an inner trochanteric primary tumor. Five patients had osteosarcoma of the humerus, two had primary osteosarcoma of the ilium, and one had a primary tumor in the first sacral vertebra. Pathologic specimens were obtained by biopsy prior to treatment and all patients had osteogenic sarcoma confirmed by pathologic examination. There were no cases of parosteal osteosarcoma included in the study.

Postoperative Adjuvant Therapy

All patients received adjuvant postoperative

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chemotherapy of adriamycin alternated with high-dose methotrexate and citrovorum factor rescue. Chemotherapy was begun 1 week following the operation and included vincristine, 1.5 mg/m^2 given iv 1 hour prior to methotrexate infusion. Methotrexate was given in an initial dose of 100 mg/kg by iv infusion. Four hours later, citrovorum factor rescue was started at a dose of 12 mg every 6 hours for 3 days. Methotrexate serum levels were measured at 12, 24, and 48 hours after the infusion. Fourteen days after the high-dose methotrexate infusion, adriamycin, 45 mg/m^2, was given as an iv bolus on each of 2 consecutive days for a total dose of 90 mg/m^2. The cycle of chemotherapy was repeated every 2 weeks until a maximum of 500 mg/m^2 total cumulative dose of adriamycin was achieved. The dose of methotrexate was increased to 200 mg/kg at the start of the second course for the remainder of the study. After the discontinuation of adriamycin, high-dose methotrexate was given once monthly for a total treatment time of 1 year. Patients in the study were randomized to receive chemotherapy alone or chemotherapy plus immunotherapy of bacillus Calmette-Guérin (BCG) (Tice strain) given by the tine technique into the areas of the axillae and the groins followed by allogeneic tumor cell vaccine into the same sites. The tissue culture vaccine was derived from skeletal soft tissue sarcoma specimens from three patients and was injected at a total dose of 1×10^8 cells. Immunotherapy was given once every 2 weeks for 3 months and then once monthly for a total treatment time of 2 years.

Preoperative Therapy

In this group of 17 patients, three elected to have amputative surgical procedures. Although amputation was advised as the standard accepted surgical procedure for all the patients, 14 elected to participate in the experimental preoperative chemotherapy and en bloc resection protocol. In the case of the sacral lesion this treatment was not possible and radiation therapy was the treatment of choice. Thus, 13 patients were treated with preoperative intra-arterial adriamycin delivered after percutaneous femoral artery catheterization. The catheters were left in a large caliber vessel of the involved extremity such as the axillary arterial femoral or common iliac artery. Adriamycin was infused by a Harvard pump over 24 hours at a dose of 30 mg suspended in 50 ml of normal saline on each of 3 consecutive days for a total dose of 90 mg. Radiation therapy to the involved extremity was started immediately following the adriamycin infusion. A 6-MEV linear accelerator delivered 350 rads/day to a total dose of 3500 rads through the midplane in ten equal fractions over 12–15 calendar days. The dose delivered by this rapid fractionation is comparable to approximately 4800 rads given at standard dose fractions. Portals were posteroanterior and anteroposterior parallel opposed and both fields were treated to include the entire region of the tumor, ie, the entire thigh or arm.

En Bloc Excisions

One week following completion of radiation therapy, an en bloc surgical resection was performed (15). A 10-cm proximal margin was achieved on involved bone and all adjacent soft tissues. Major nerves and blood vessels were dissected free and preserved. The diseased bones were replaced by cadaver allografts (16,17) obtained from the tissue bank of the National Naval Medical Center, Bethesda, Md. These grafts had been sterilized by radiation and were preserved by vacuum desiccation. Grafts were fixed internally with Sampson intramedullary rods with external flutes to prevent torsion at the recipient donor interface, and, in the last five patients, methylmethacrylate cement was also used to insure stability. Patients with lower-extremity bone replacement were placed in a long leg non-weight-bearing cast for 8 weeks after which they wore a weight-bearing long leg brace with a drop lock hinged knee for up to 1 year. One patient who had a massive osteosarcoma of the left ilium was treated by excision only, with no allograft replacement. This patient can ambulate with crutches and bear approximately 60 lb of weight on the involved extremity.

RESULTS

Figures 1 and 2 display the cumulative percent recurrence and survival rates for this group of patients. Of the 17 patients treated thus far, a cumulative percent survival of 60% has been achieved. Three patients had recurrence of their disease; one had local recurrence in the tibia following a femoral resection but now is disease-free following an above-the-knee amputation, a second developed metastatic osteogenic sarcoma to a localized area of the lung and is free from disease after pulmonary resection, and the third had unresectable distant pulmonary disease. The remainder are alive and free of recurrence. An earlier series of 16 patients treated by amputation alone at UCLA from 1970 to 1973, before effective chemotherapy was available, had no survivors. Presently, 85% of the patients treated in our series remain alive. Only one patient died from disseminated osteosarcoma. The median followup times for the two groups of

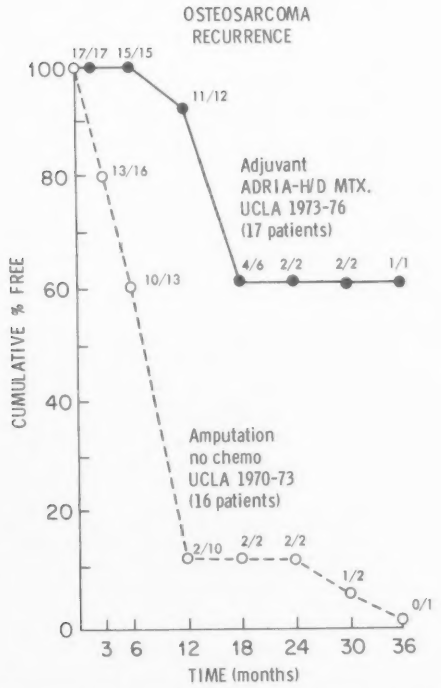

FIGURE 1.—Life-table analysis for proportion of patients free of recurrent disease. Vertical axis = cumulative % of patients free of disease. Horizontal axis = time since the operation. Nos. separated by slash (/) = No. of patients who remained free of disease/No. of patients at risk of disease recurrence during that time period.

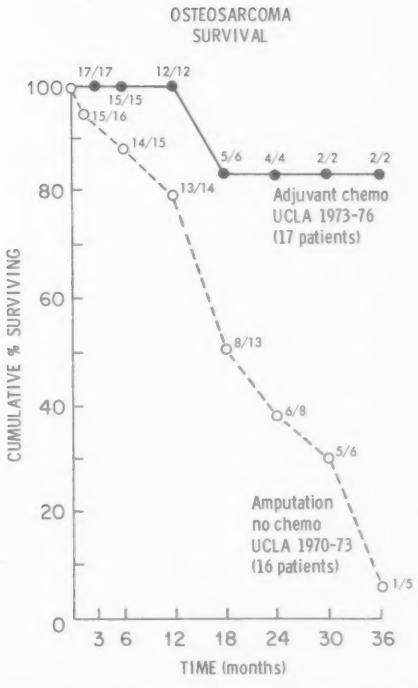

FIGURE 2.—Life-table analysis for survival. Vertical axis = cumulative % of patient survival. Horizontal axis = time since the operation. Nos. separated by slash (/) = No. of patients surviving/No. at risk of disease recurrence during that time period.

patients are given in table 1. The median followup time for patients who had amputation is 11 months, for limb salvage, 11 months, and for radiation therapy with no operation, 6 months.

Comparison between the two randomized groups of patients receiving adjuvant chemotherapy or chemoimmunotherapy is not possible at this time, but table 2 lists our results to date. Although some advantage is noted in patients receiving the additional immunotherapy, the median followup time of the two groups is not comparable.

One of the more dramatic findings in this study can be found in the histologic comparison of specimens from 14 patients treated by amputation alone to those from 12 patients treated by preoperative intra-arterial adriamycin and radiation therapy (table 3). Tumor cell necrosis was defined as total absence of identifiable nuclei, and at least 15 representative samples were examined for these comparisons. Evaluations were made without prior knowledge of the type of treatment. The absence of necrosis in the specimens from amputation ranged from 0 to 30%, with an average of 10% of the cells showing no nuclei. Specimens from patients treated with preoperative therapy averaged 86% necrosis (60%–100%) and four of 12 specimens displayed no identifiable nuclei.

Functional results from bone grafts cannot be ascertained at this time. However, results from the upper-extremity grafts appear to be excellent. These patients have normal function of the hand and realize normal sensations. Function in the patients with lower-extremity grafts is much more restricted in that knee motion is limited, although there is intact sensory and joint function at the hip and ankle.

Although median followup of our series of 17 patients with osteosarcoma is short-term, certain general conclusions can be made from this study. First, it is apparent that patients treated by the adjuvant chemotherapy remain disease-free for a much longer time than those treated by our institution before the advent of effective chemotherapy. There have been, and most likely will continue to

TABLE 1.—Osteosarcoma: influence of treatment of the primary on disease status

Treatment	Total No. of patients	No. of patients disease-free (%)	Median mos of followup (range)
Amputation	4	3(75)	11(5–30)
Limb salvage	12	10(83)	11(2–21)
Radiation (no surgery)	1	1(100)	6
Totals	17	14(82)	11(2–30)

TABLE 2.—Osteosarcoma: adjuvant chemotherapy vs chemoimmunotherapy*

Treatment	Total No. of patients	No. of patients disease-free (%)	Median mos of followup (range)
Chemotherapy alone	10	7(70)	12(4–29)
Chemotherapy + BCG + tumor cell vaccine	7	7(100)	7(2–30)

*BCG + allogeneic tissue culture vaccine.

TABLE 3.—Osteosarcoma: effect of preoperative therapy on histology

Treatment	Total No. of patients	% necrosis (range)	
		Pretreatment biopsy	Postoperative specimen
Amputation	14	9(0–30)	9
Intra-arterial adriamycin, radiation, radical excision	12	10(0–30)	86 (60–100)*

*4 of 12 specimens had no viable tumor cells.

be, disease recurrences in this group of patients, although a high percentage regained their disease-free status after additional surgical procedures. Whether immunotherapy is additive to chemotherapy in terms of improving the results remains to be seen. There is dramatic histologic evidence of tumor cell destruction by pretreatment with adriamycin and radiation therapy in this group of patients. Although this tumor cell necrosis cannot be equated with the biologic potential of cell regrowth, the histologic evidence of tumor cell death and the effectiveness of adjuvant therapy is certainly evident. Finally, it is impossible to predict the long-term function of the allografts at this early date, but these allografts seem to be a reasonable alternative to bone replacement with metallic prosthesis or amputation. Definite results can only be obtained by a longer period of followup for these patients.

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Local En Bloc Resection for Limb Preservation [1]

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SUMMARY

Preoperative treatment with four to eight weekly courses of high-dose methotrexate, citrovorum factor rescue, and vincristine was administered to ten patients with osteogenic sarcoma involving the distal femur (five patients), proximal tibia (three), proximal humerus (one), and tibial diaphysis (one). Five of the patients also received intra-arterial adriamycin (ADR) (45–75 mg/m^2) administered over 6–72 hours at the beginning or end of treatment. Clinical responses were obtained in eight patients. Pre- and post-angiographic studies permitted the following assessment of response: distinct improvement in three patients, mixed response (regression of tumor neovascularity in some areas and increase or persistence of neovascularity elsewhere) in four, no change in one, and possible deterioration in two. Three patients developed complications associated with intra-arterial ADR, one of whom required amputation. An amputation was also performed in another patient because of inadequate control of the primary tumor during preoperative treatment with chemotherapy. Local en bloc resection was performed in the remaining eight patients with insertion of internal prostheses. There were no local recurrences. However, sepsis, which was successfully treated, developed in one patient and complications with wound healing developed in two others. All patients currently retain their prostheses. Excellent function in the patient with the upper limb prosthesis has been achieved, but the function of the salvaged lower extremities over extended periods of time must still be determined. The procedure is a major challenge and should only be performed in centers where the necessary skills, resources, and commitments are available.

[Cancer Treat Rep 62:217–223, 1978]

The Sidney Farber Cancer Institute and Children's Hospital Medical Center commenced studies to determine the feasibility of limb preservation for patients with osteogenic sarcoma in 1975. The impetus to undertake such investigations was provided by the encouraging results achieved with high-dose methotrexate (MTX) and adriamycin (ADR) in the management of micrometastases and established disease (1–7) (*see* companion paper in this issue by Jaffe et al) and by the successful demonstration of en bloc resection and prosthetic replacement of bone by Rosen et al (8). However, in the experience reported herein, local en bloc resection rather than total bone replacement, as reported by Rosen et al, was performed. This required construction of individually measured prostheses. Because manufacture of such prostheses required several weeks, preoperative chemotherapy was administered during the delay. This conceivably could also produce destruction of the primary tumor and micrometastases. We present our preliminary results in this report.

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MATERIALS AND METHODS

Eligibility for Entry

A. Attainment of complete or nearly complete physical growth for patients with lesions of the lower extremities.

B. Safely resectable lesion. The major artery did not show tumor encasement on the angiogram although gradual displacement of the vessel by tumor was not considered a contraindication.

C. Absence of demonstrable metastases. Although the presence of metastases was not necessarily considered a contraindication, it was elected to re-evaluate recommendations for this procedure after observing the response of the metastases to chemotherapy. Absence of responses might be considered a strong contraindication.

D. Full apprisal of patients and parents as to the procedure. Since this was of an investigational nature, limb ablation might still be required at any stage because of failure or other complications.

Patients (Table 1)

Ten patients were entered into the program from January 1975 to December 1976. Their ages ranged from 13 to 18 years. Five patients had primary lesions of the distal femur, four of the proximal or middle tibia, and one of the upper humerus. No patient had roentgenographically visible pulmonary or bone metastases at initiation of treatment. All had measurable soft tissue involvement of variable degree.

The patients were subjected to a full physical examination, pulmonary tomograms, angiographic studies of the tumor, radionucleide bone scans and anthropometric radiographs, and measurements of affected limb for manufacture of a suitable endoprosthesis. The results were correlated and the feasibility of performing a local en bloc resection was determined. An affirmative decision was fol-

TABLE 1.—Response to treatment

Patient No.	Age (yrs)	Site of primary	No. of V-MTX-CF courses	Intra-arterial ADR infusion during preoperative treatment (mg/m²)		Response*		% viable tumor	Evidence of pulmonary metastases (mos)	Followup (mos)	Comments
				Beginning	End	Clinical	Angiographic				
1	18	Proximal humerus	4		70	+	+	10		23	
2	13	Proximal tibia	4		75	+	Mixed	10	Yes (13)	17	ADR slough—amputation
3	16	Proximal tibia	8			+	+	20		12	Ulcers over prosthesis
4	17	Proximal tibia	8			–	–	90	Yes (6)	12	Small wound dehiscence
5	15	Tibial diaphysis	6			+	No change	10–20		9	Dislocation, distal end of prosthesis—recemented
6	16	Distal femur	8			+	Mixed	60	Yes (6)	9	Sepsis—successfully treated
7	18	Distal femur	8			+	Mixed	50		9	
8	14	Distal femur	8	75	75	+	+	0		6	ADR skin reaction—healed
9	16	Distal femur	2	45		–	Mixed	50		5	Possible local "escape"—amputation
10	16	Distal femur	8	75		+	–	90		1	ADR skin reaction—healed

* + = distinct improvement; – = no improvement, possible deterioration; mixed = regression of tumor neovascularity in some areas and increase or persistence of neovascularity elsewhere; no change = hypovascular tumor, no change in tumor size pre- and post-angiography.

lowed by requisition of a suitable prosthesis and definitive entry into the program.

Procedure

The limb preservation program comprised four basic components:

1. weekly courses of vincristine, high-dose MTX, and citrovorum factor (V-MTX-CF);
2. intra-arterial ADR;
3. local en bloc resection; and
4. insertion of an internal prosthesis.

Weekly V-MTX-CF.—Full details of the V-MTX-CF program are outlined in the companion paper in this issue by Jaffe et al. In the initial study, four weekly doses of V-MTX-CF were administered (5). Subsequently, after the safety of the procedure was determined and since, in several instances, a suitable endoprosthesis had not been manufactured after 4 weeks, the number of courses was extended to eight. Following the last V-MTX-CF course, a repeat angiographic study was performed.

Intra-arterial ADR (table 1).—In five patients, intra-arterial ADR was administered by a Harvard pump 24 hours preceding the first or final V-MTX-CF infusion. The doses varied from 45 to 75 mg/m^2 and were administered over 6 hours in four patients and over 72 hours in the fifth patient (No. 2).

Local en bloc resection.—This operation was performed 10–14 days after the completion of chemotherapy, provided the hemogram was normal and no complications had developed. Each tumor was resected with wide margins. Seven centimeters of bone proximal to femoral lesions or distal to tibial or humeral lesions were removed—the limit of the tumor was estimated by bone scan. The entire knee joint including the patella, all ligaments, and suprapatellar arch was removed in each lower-extremity tumor. Femoral lesions included the proximal tibia just proximal to the infrapatellar ligament. Tibial lesions included sufficient distal femur to be just proximal to the suprapatellar pouch. Active extension of the knee was made possible by transferring the hamstring muscles anteriorly. The humeral lesion was resected together with the scapula and shoulder joint and the proximal one half of the humerus.

Internal prostheses.—A variety of prostheses was used. Knee joints were modified Guepar knees with solid segments designed to replace the resected bone. Individual prostheses were made because of the varying sizes required for children. These prostheses took approximately 8 weeks for individual manufacture. The Guepar knee was chosen because it is intrinsically stable in extension. One tibial tumor in an obese boy (125 kg) was replaced with intramedullary Kuntscher rods plus steel mesh and methyl methacrylate cement. Following resection of the humeral lesion, the humerus was stabilized with a Buchholz shoulder prosthesis modified with a segment of Kuntscher rod to give adequate length for the resected bone and the glenoid component was cemented into the residual clavicle. Allografts were not used because our experience shows that bone grafts are extremely slow to heal when chemotherapy is used.

Patients were treated with iv antibiotics during the operation and more recently postoperatively for 1 week. Oral antibiotics were then prescribed for varying periods of time until complete healing and the absence of infection were demonstrated and chemotherapy was concluded. The limbs were immobilized for 2–3 weeks and gradually allowed motion. Full weight bearing was permitted as soon as the patients could stand comfortably, usually at 5–7 days. Adjuvant chemotherapy with V-MTX-CF-ADR was initiated 3 weeks after the operation. More recently, postoperative chemotherapy has been modified to include an intensive course of four weekly V-MTX-CF treatments before commencing V-MTX-CF-ADR.

RESULTS (Table 1)

In eight of the ten patients, subjective and objective improvements were noted on clinical and radiographic examination. The clinical responses were characterized by complete or nearly complete disappearance of pain, reduction in tumor size, improved mobility, and reduction in local temperature within 2–3 weeks. In patient 4, the tumor remained stationary and only slight reduction in pain was noted. In patient 9, a new subcutaneous nodule developed adjacent to the primary tumor approximately 3 weeks after initiation of treatment. No patient developed pulmonary metastases during the period of preoperative intensive chemotherapy.

Angiographic evidence of response generally comprised reduction or disappearance of tumor neovascularity. Other changes, including increasing staining, presumably due to capillary or arteriovenous shunting following tumor vessel alteration, were also observed. A mixed response was considered to be present when tumor neovascularity regressed in some areas and increased or persisted in others. Correlation between angiographic responses and extent of viable tumor seen on pathologic examination of the resected specimens was attempted in all patients. The results are outlined in table 1. An example of the angiographic response in patient 5 with osteogenic sarcoma of the distal femur is

outlined in figure 1 and the corresponding histologic features are outlined in figure 2 (A and B).

Intra-arterial ADR was associated with complications in three patients. An area of brawny induration and erythema approximately 5 cm below the tip of the catheter occurred 24 hours following initiation of the infusion in patient 2. Examination with a Wood's lamp failed to reveal evidence of fluorescence and the infusion was maintained. Two weeks later, however, sloughing of the indurated area occurred; local resection was not considered possible and an amputation was performed. A similar phenomenon occurred in patients 8 and 10 with the first and second intra-arterial infusions, respectively. Fortunately, satisfactory wound healing occurred permitting local en bloc resection within 8–10 weeks of initiation of treatment. Amputation was performed in the patient who developed a subcutaneous nodule during preoperative chemotherapy.

Of the eight patients who underwent prosthetic limb replacement, local recurrence was not observed. However, one patient developed a staphylococcal infection approximately 3 months postoperatively. This was treated successfully by debridement and antibiotics, leaving the prosthesis in place. One patient developed a wound slough at the site of the previous biopsy which had been performed elsewhere transversely to the long axis of the leg, resulting in a cross-shaped closure. This healed slowly over 8 months. A third patient developed an ulcer over the prosthesis, requiring a cross-leg pedicle flap for closure,[3] and a fourth patient developed displacement of the distal end of a tibial prosthesis which was recemented. Despite these complications, the patients still retain their prostheses. They are able to ambulate without assistance although minimal flexion of the knee is present in three of the

[3]Which failed and required amputation.

FIGURE 1.—*Left:* Arteriogram in patient with osteogenic sarcoma of the distal end of the femur. A densely vascular circumferential tumor of the distal diaphysis and metaphysis with a large soft tissue component is noted. There is posterior deviation of the popliteal artery without encasement or other complication. *Right:* Posttreatment angiogram. Tumor vascularity and size have dramatically diminished. The popliteal artery has assumed a more normal anatomic position. This was accompanied by complete subjective improvement.

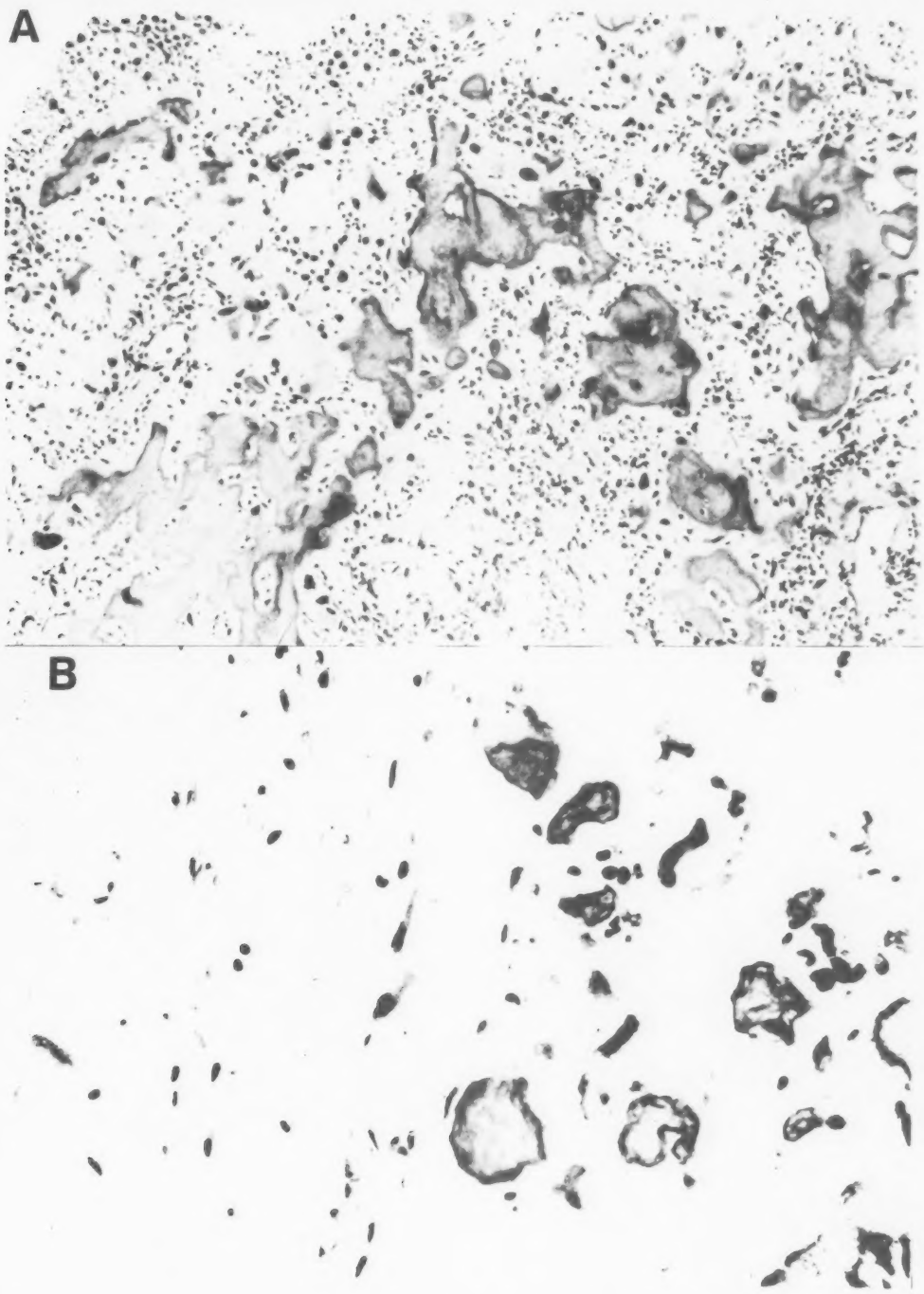

FIGURE 2.—A. Section of tumor prior to initiation of treatment. Intramedullary osteoid tissue and malignant cells characteristic of osteogenic sarcoma are present in this predominantly cartilaginous tumor. B. Posttreatment section. Intramedullary neoplastic residual osteoid and chondroid tissue is apparent. Intervening tissue is poorly cellular and contains only rare atypical cells.

five patients who had knees replaced with hinged prostheses. The full potential of these procedures must await further observation. The patient who underwent local en bloc resection of the upper humerus achieved full function at the elbow, forearm, and hand, with stability at the shoulder (fig 3).

During the period of subsequent adjuvant chemotherapy, three patients, including one who had amputation, developed isolated pulmonary metastases at 6, 6, and 13 months, respectively. In the patient who had amputation, the metastasis has been removed and the others are undergoing multidisciplinary treatment with similar intent.

DISCUSSION

Local en bloc resection as primary definitive treatment is not a new therapeutic concept. It has been successfully employed in patients with benign and less aggressive malignant tumors where the potential for local occurrence and dissemination is minimal. Such circumstances did not obtain in osteogenic sarcoma where pulmonary metastases were considered to be present in $> 80\%$ of patients at diagnosis. However, the procedure became a logical sequence with the availability of effective chemotherapy which conceivably could destroy such micrometastases during treatment of the primary tumor.

A possible drawback to the limb-preservation program is the risk of developing metastases (if these had not previously occurred) or the selection of drug-resistant cells during the preoperative treatment. However, pathologic examination of the resected specimen might help in the selection of appropriate chemotherapy for the adjuvant program. Thus, evidence of major tumor destruction would provide strong incentive for the continued use of the previously administered agents; failure to document such effect would be an indication to investigate alternative treatment. This concept presupposes that the destruction of microscopic disease and bulk tumor is governed by similar factors. A wider experience is required to test the validity of these hypotheses.

Patients should only be considered candidates for limb preservation if the primary tumor appears locally resectable ab initio. Thus, chemotherapy should not be instituted to render a suspected inoperable tumor operable. Similarly, any evidence of "escape" or failure of local control during preoperative treatment should be followed by immediate amputation.

Angiographic studies should only be employed as ancillary investigations. The results should not be utilized to interpret extent of tumor destruction. For example, erroneous conclusions may be drawn from increased stainings which may be due to resistant tumor neovascularity or to capillary arteriovenous shunting following tumor destruction. More detailed correlation between the angiographic

FIGURE 3.—Patient who had local en bloc resection of upper humerus; he achieved full function at elbow, forearm, and hand, with stability at shoulder.

investigations and pathology studies is in progress.

Intra-arterial ADR may have improved the extent of local tumor destruction. This procedure, however, is not without risk. Erythema and subsequent necrosis of tissues may prevent the possibility of resection. The cause of the ulceration and skin necrosis is presently undetermined. Selective entry of the drug into a small vessel has been implicated and it has been suggested that it may be prevented by positioning the catheter in a large-caliber vessel proximal to the tumor.[4] Intra-arterial ADR is currently undergoing review and cannot be recommended with confidence until more information is accumulated.

Initial results in the limb-preservation program are promising but the function of the salvaged lower extremities over extended periods of time must still be determined. Upper-extremity preservation is markedly better than any external prosthetic device attempting to replace a forequarter amputation. Because of possible escape during preoperative treatment or other complications, the patient and medical attendants must be prepared to accept amputation as an alternative. The procedure remains a major challenge and in view of its investigative nature, it should only be performed in centers where the necessary skills, resources, and commitments are available.

[4] Morton D. Personal communication.

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En Bloc Resections for Osteogenic Sarcoma

Ralph C. Marcove[1,*]

Preservation of a limb, without sacrificing the principles of cancer surgery, is a desirable goal in young people with osteogenic sarcoma. At the present time, amputation is regarded by most authorities as the only well-established typical curative treatment for this malignancy (1–6). Usually for a tumor close to a joint, amputation includes excision of a part of the adjacent joint bone as well as a wide removal of the involved bone to encompass both area of potential capsular local spread and possible intra-osseous skip areas of tumor. The distal femur lesion (having the lowest cure rates) usually requires removal of the whole bone (7).

The following study was undertaken to determine whether en bloc resection in association with intensive chemotherapy is a realistic alternative to radical amputation and chemotherapy (8–14). The purpose of this paper is to present a preliminary report on 43 patients who underwent en bloc resection for osteogenic sarcoma of the femur (20 patients), tibia (11 patients), shoulder girdle (11 patients), and fibula (one patient).

MATERIALS AND METHODS

All patients had routine history, physical examination, and laboratory determinations. Standard anteroposterior and lateral roentgenograms of the involved bone as well as skeletal survey, bone scan, and chest tomography were performed. Biplane arteriography of the area involved with osteogenic sarcoma was done (15,16). All data were evaluated to determine size, location, and resectability of the tumor and the soft tissue component as well as the presence or absence of metastatic disease or skip areas. In children with distal femur lesions, orthoroentgenographic scanograms of the lower extremities and appropriate studies to determine the degree of skeletal maturity and projected growth curves were also done. The objectives and potential risks of the protocol were carefully explained to the participants and their families. The presence of pulmonary metastases was not necessarily a contraindication as long as the lesions appeared surgically resectable (17–20) and/or responsive to chemotherapy (14,21,22). The advisability of using an ischial weight-bearing brace postoperatively was discussed with the parents and patients before surgery.

DISTAL FEMUR LESIONS

Once the initial workup, including scanograms and routine physical and roentgenographic examinations, is complete, construction of the metal total femur with a total knee prosthesis begins, taking approximately 8 weeks. During this time the patient is maintained on a chemotherapeutic regimen consisting of vincristine, adriamycin, and high-dose methotrexate with citrovorum factor rescue (14,21,22). When the prosthesis is ready the patient is re-evaluated; if the protocol criteria are still valid, the replacement is performed. After sufficient postoperative wound healing, adjuvant chemotherapy resumes (biweekly cyclophosphamide, vincristine, high-dose methotrexate with citrovorum factor rescue, and adriamycin for five cycles). Immediately after surgery, the patient is placed in a long-leg ischial weight-bearing brace (at first with a pelvic band) and started on an active range of motion as well as ambulation as the clinical situation allows. The pelvic band portion is removed in about 6 weeks.

Operative Technique

A lateral biopsy approach was used in previously untreated cases where this was subsequently the proposed site of the surgical incision. Through a long Gibson skin incision, posterior and anterior approaches are made into the hip on the affected side. The incision itself is carried along the greater trochanter down to the lateral aspect of the femur distal to the knee and then curved slightly anteriorly over the proximal lateral tibia to extend 4 cm distal to the tibial tubercle; the previous biopsy scar and tract are included in the surgical resection. The incision is carried through the layers and as the resection nears the area of tumor, ample margin is left on the femur so that tumor is never seen. If tumor pseudocapsule is seen during surgery, the operation is discontinued and after a change of

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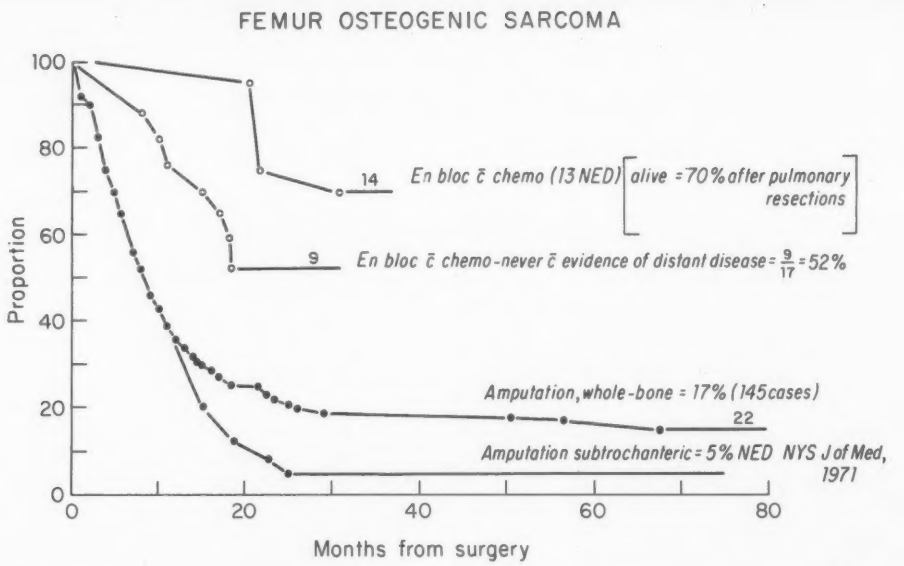

FIGURE 1.—Comparison of amputation treatment to en bloc femur resections on 20 patients with chemotherapy ± pulmonary surgery (17 patients admitted with local disease).

instruments a higher level of amputation is performed. (This happened once.) The knee is removed en bloc with the distal femur. The patella tendon is maintained intact and the patella is split coronally so that the inner half stays with the specimen and the outer half remains in continuity with the remaining quadriceps mechanism. The tibia is reamed to accept the stem of the total-knee prosthesis and methyl methacrylate is placed in the tibia after a trial reduction of the prosthesis. The glutei are attached with heavy silk through preformed holes in the prosthetic shaft proximally and the medial and lateral thigh musculature are attached to each other. The distal hamstrings are often transferred anteriorly to act as knee extensors and to help give a deep layer below the skin incision. The wound is carefully checked for hemostasis (cautery is usually not used), and closure with hemovacs is accomplished. The patients receive prophylactic antibiotics preoperatively and postoperatively. The wound is flushed with local antibiotics during and immediately after surgery. Legs are elevated postoperatively.

Results

Twenty-six patients with distal femur lesions were originally considered for replacement surgery (23). Of these, five patients started the protocol as described, but because of the tumor size, amputations were performed. One patient had amputation at the time of surgery since tumor pseudocapsule was encountered.

As shown in figure 1, the 20 remaining patients, ages 11–21 years, have a followup of 2–35 months. Thirteen patients (65%) are alive disease-free; one patient is alive with disease. Nine patients (52%) of 17 who were admitted disease-free to the protocol are still without disease.

Of the three patients admitted originally with pulmonary lesions, one is alive without disease at 24 months after replacement (she also had a second pulmonary metastasis and thoracotomy at 7 months after replacement) and the remaining two died at 21 and 30 months, respectively, with widespread metastases. Six patients had thoracotomies; 50% are alive without disease. One patient had a negative exploratory thoracotomy after chemotherapy shrunk her nodule.

Seven patients needed amputations: three for infection, two for local recurrence, one for prosthesis breakage, and one for radiation necrosis (6600 rads were given prior to replacement). Three of this group are alive disease-free: one had infection, one had local recurrence, and one had mechanical failure.

Functional Results

Walking progressed from crutches to a cane. Without a cane a gluteus-maximus limp is observed

unless an ischial weight-bearing brace is used. The range of motions usually improves with time; the ankle and foot motion was usually quite good. Patients are instructed to wear the ischial weight-bearing brace with quadrilateral socket and to treat the extremity much the same as a "polio leg."

SHOULDER GIRDLE LESIONS

The Tikhoff-Linberg procedure (en bloc upper humeral interscapulothoracic resection) is an alternative to radical ablation for neoplasms of the shoulder girdle (24–30). The main indication for resection is that the neoplasm does not involve the axillary artery or the brachial plexus, lymph nodes are negative, and the neoplasm is not fixed into the chest wall. Primary tumors of bone, as well as soft tissue tumors adjacent to the bone, can be treated by this method. A forequarter amputation (5,30) is probably a better operation however, if the lymph nodes are involved.

Operative Techniques

The initial incision is made overlying the inner two thirds of the clavicle and then extending from the region of the coracoid distally along the medial border of the arm overlying the neurovascular bundle. Posteriorly one extends longitudinally in the mid-scapular region. The incision is altered so that the biopsy scar and tract are excised with the specimen. If the neurovascular bundle is free of tumor, then the mobilization of the neurovascular bundle continues. The musculocutaneous and radial nerves can be identified and are usually preserved. However, if the lesion involves the soft tissue in the nerve vicinity of the proximal humerus, the radial nerve may have to be sacrificed along with the musculocutaneous nerve. In one patient, even the ulnar nerve was removed, the hand having only the medial nerve. The posterior skin incision originates at the lateral one third of the clavicle line and is carried posteriorly and longitudinally along the mid scapula to the angle of the scapula. The inferior angle of the scapula is mobilized and the entire vertebral border is resected from the chest wall much the same as the plane developed in the forequarter amputation. For lesions of the scapula, care must be taken to maintain a wide soft tissue margin. The skin flap from the initial incision is raised over the proximal humerus leaving the deltoid intact with the specimen in upper humeral lesions. When much humerus is removed, excessive shortening can be avoided and better elbow power for flexion can be provided by a humeral prosthesis or Kuntscher nail replacement fixated into the proximal soft tissue or clavicle stump. Some patients are more comfortable if a greater residual amount of clavicle is removed and if nail fixation is into the soft tissue. Hemovacs are placed in the wound and closure is routine. A postoperative sling and swathe or Valpeau dressing is employed. Hand and elbow range of motion is encouraged early postoperatively.

Results

Thirty-seven Tikhoff-Linberg procedures have been performed. Eleven of these cases were done for osteogenic sarcoma (31). These patients ranged in age from 8 to 63 years, and their tumor was in the shoulder girdle (upper end of the humerus, scapula, and clavicle). Followup is from 2 to 37 months. Seven patients (63%) are alive without evidence of disease (*see* fig 2). One patient of this group was admitted with pulmonary metastasis and subsequent thoracotomies were performed at 2, 7, and 13 months after resection. He is now without evidence of disease 3 months later.

Of the four patients who died, one was admitted with pulmonary metastasis (radiation osteogenic sarcoma from a previous Hodgkin's disease) and died of widespread metastatic disease 6 months after resection. Surgery in this case was for palliative purposes only. Another patient died 7 months after resection with widespread disease and a local recurrence. The remaining two patients died of widespread metastasis.

The condition of the one patient with local recurrence could not have been improved by a forequarter amputation since the same tissue planes would have given trouble (at the levator scapula). Six patients (66%) never had any evidence of distant disease. One patient who is alive in this group without disease was given postoperative vaccine (lysed cell) therapy 4 years ago. Only five patients in this group were included in the chemotherapy program and all are free of disease, including the one patient who had three thoracotomies.

Functional Results

The wrist and hand functions are normal in this group. In those with radial nerve palsy, a cock-up splint was used and tendon transfers were done 2 years later. A small amount of shoulder padding usually corrects the surgical deformity when wearing clothing, but a plastic filler is ideal for wearing clothes.

PROXIMAL TIBIA LESIONS

As in patients with lesions of the shoulder girdle

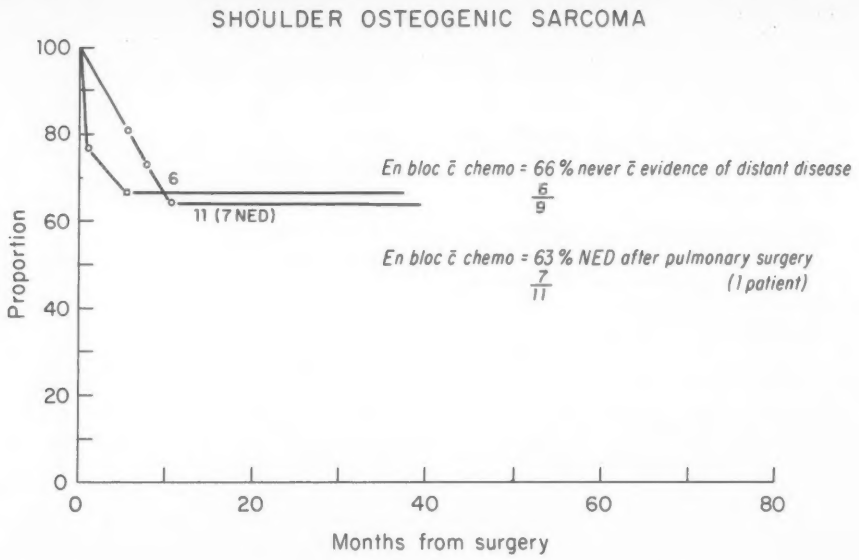

FIGURE 2.—En bloc shoulder resections (11 patients) (Tikhoff-Linberg procedure) with chemotherapy ± pulmonary surgery.

and distal femur, an appropriate preoperative workup is done to determine resectability of the proximal tibia lesions. This again includes bone age studies, chest tomography, and biplane arteriography. Skeletal survey and bone scans are done to rule out any distant lesions. After the en bloc resection and total long-stem knee replacement, patients begin receiving the chemotherapy protocol (9,14,21).

Operative Technique

A posterior medial incision is made and the neurovascular bundle is identified. The anterior tibial artery as well as other interosseous perforating vessels are ligated at the posterior tibial vessel. The popliteal fossa vessels are also ligated preserving the main stem. The fibula is removed en bloc along with the upper tibia (for tumor in the latter) because of its proximity. The total knee-distal femur is also removed en bloc, keeping a margin of normal tissue planes around the tumor. Care must be taken to preserve cutaneous nerves. If the upper tibia in the subcutaneous region has tumor growing into the skin, this area, of course, must be sacrificed. The long-stem Guepar knee (with solid shafts) is cemented into the residual distal tibia and proximal femur.

Results

Eleven patients, ages 11–24 years, with lesions of the proximal tibia and a followup of 4–23 months were included in this group. Eight patients (72%) never had any evidence of distant disease. Two patients are alive with disease; the followup period has been 16 and 20 months after resection, respectively. One patient died at 3 months after surgery with pulmonary metastasis and local recurrence; her lesion was too large (in retrospect). One patient had an amputation at his request because of excessive numbness of his foot (too many cutaneous nerves had been sacrificed) (*see* fig 3).

FIBULA LESION

A 15-year-old girl with a history of sustaining a direct blow below the right knee 3 weeks prior to admission and continuing mild discomfort and swelling was referred to our institution. Roentgenograms revealed an osteogenic sarcoma of the right fibula. The right knee joint had a full range of motion. Clinically, the lateral popliteal nerve was intact. Further routine workup was normal and an arteriogram showed resectability of "tumor." She was given the chemotherapy regimen and had surgery performed on September 30, 1974, after a frozen section biopsy.

Operative Technique

A long skin incision was made from above the knee joint to the ankle leaving a segment of skin directly overlying the tumor. Skin flaps were devel-

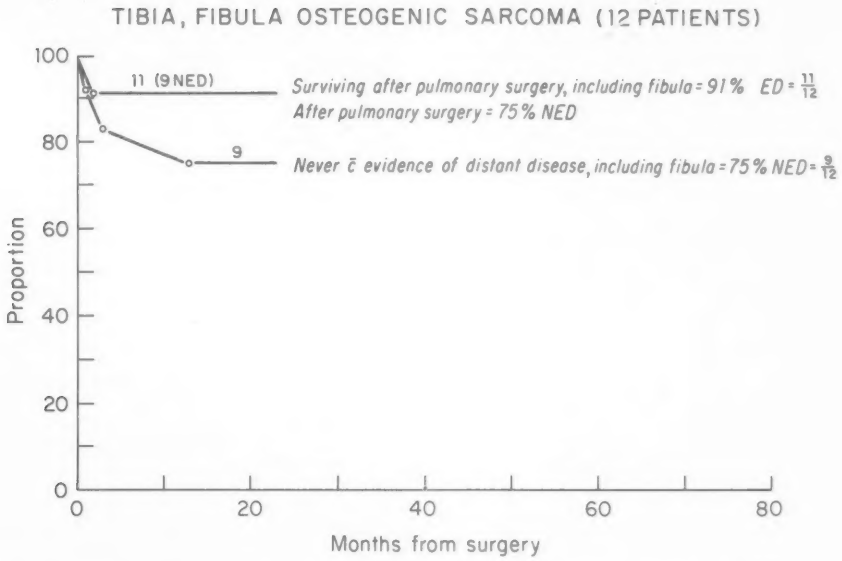

FIGURE 3.—En bloc tibia (11 patients) and fibula (1 patient) resections with chemotherapy ± pulmonary surgery.

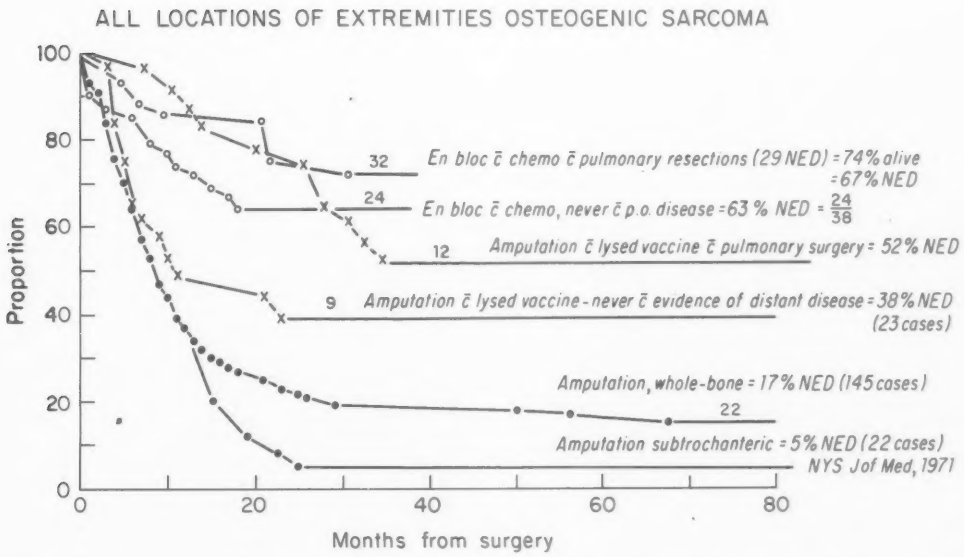
ALL LOCATIONS OF EXTREMITIES OSTEOGENIC SARCOMA
32
En bloc c chemo c pulmonary resections (29 NED) = 74% alive = 67% NED
24
En bloc c chemo, never c p.o. disease = 63% NED = 24/38
12
Amputation c lysed vaccine c pulmonary surgery = 52% NED
9
Amputation c lysed vaccine - never c evidence of distant disease = 38% NED (23 cases)
Amputation, whole-bone = 17% NED (145 cases)
22
Amputation subtrochanteric = 5% NED (22 cases)
NYS Jof Med, 1971
Proportion
Months from surgery
0
20
40
60
80
100

FIGURE 4.—Comparison of amputation treatment to en bloc resections on 43 patients with chemotherapy ± pulmonary surgery.

oped anteriorly and posteriorly. Dissection was deepened. Again the tumor was never encountered, and a 2-cm normal margin was left over the tumor. (Consent had been obtained for a mid-thigh amputation if the tumor pseudocapsule was seen.) The lower fibula was disarticulated at the ankle mortice. Using an osteotome, a rim of tibia above and medial to the tibio-fibula joint, including part of the lateral tibial condylus, was removed en bloc with the specimen. Thus, an "en bloc" of the whole of the fibula was removed with tumor, tibio-fibula joint, and a wide surrounding margin of muscles; the common peroneal nerve and two of three lower limb arteries were ligated. A long-leg plaster of Paris cast was applied with the ankle in the neutral position for 6 weeks. Later stress views showed no instability.

Results

Because of persistent fluid collection, chemotherapy was delayed until 2 months' postoperatively. Vincristine, methotrexate, and citrovorum factor rescue were given according to our adjuvant chemotherapy protocol (14,21,22). This continued for 1 year. This patient now walks without a limp with a drop foot brace, and was free of disease for $2^1/_2$ years. A nodule then developed inside the upper tibia and, therefore, the remaining upper tibia was removed en bloc; a Guepar total knee with long-stem prosthesis was inserted. She is well postoperatively. There is good stability of the ankle joint. The residual capsule as well as the lateral ligaments contribute to the lateral stability of the ankle joint (fig 3).

CONCLUSION

In all, 43 patients have been treated for osteogenic sarcoma of the extremities by en bloc resection and chemotherapy, with pulmonary resections. Seventy-four percent of this group are alive after tumor resection, chemotherapy, and pulmonary resections; to date, 67% are alive without disease after the above treatment (*see* fig 4).

Of the 38 patients (five excluded because of initial presentation with pulmonary lesions), 63% (24 patients) are alive without evidence of disease, never having had postoperative distant disease manifestation. When compared to published survival curves, these results are considerably better than previously described treatment plans (no evidence of disease was seen in 52% of patients after amputation, lysed cell vaccine, and pulmonary surgery, in 38% after amputation and lysed cell vaccine [with no evidence of distant disease], in 17% after whole-bone amputation, and in 5% after subtrochanteric amputation) (*see* fig 4).

The ultimate test for this surgery is the control of tumor. The mean time for developing pulmonary metastases after amputation for osteogenic sarcoma previously reported was 7.9 months (32). In a recent study at Memorial Hospital when roentgenograms were taken more frequently postoperatively (1-month intervals), the mean time for detecting pulmonary metastases was 5.5 months. Poor survival statistics in childhood osteogenic sarcoma, in spite of adequate radical ablation of the primary tumor site, are probably due to the presence of distant microfoci of disease, mainly pulmonary, at the time of surgery (33,34). Hence, there is a need for pulmonary resections and systemic chemotherapy utilizing drugs with demonstrated efficacy in this radioresistant tumor.

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"Single"-Agent Activity of High-Dose Methotrexate With Citrovorum Factor Rescue

Daniel D. Von Hoff,* Marcel Rozencweig, Arthur C. Louie, Richard A. Bender, and Franco M. Muggia [1,2]

Experimental animal tumor data suggest that the therapeutic effectiveness of methotrexate (MTX) might be somewhat increased by administering high doses requiring citrovorum factor (CF) rescue (1). However, the alleged superiority of the high-dose regimen (HDMTX-CF) over conventional lower doses of the drug has not been clearly established in man. In fact, there is no agreement on how high the dose of MTX should be, and the optimal dose schedule of CF administration remains to be defined. In addition, prudent use of the high-dose regimen requires facilities for monitoring serum levels of the drug and, even under the best circumstances, drug-related deaths occur (2). At this point, it is unclear whether the incidence of these deaths is higher than that seen with conventional doses of MTX. Currently, the number of clinical trials with HDMTX-CF is rapidly increasing and should indicate, in the not too distant future, whether the cost, risks, and practical difficulties of this therapeutic approach are actually justified.

This review briefly summarizes the published data on the antitumor activity of the HDMTX-CF regimen. Hopefully, the information will provide some insight into areas worthy of further investigation.

MATERIALS AND METHODS

For the purposes of this report, HDMTX is defined as doses > 1 g/m^2 or 25 mg/kg/course of treatment (3). The analysis is based on published results of phase II studies on the value of HDMTX-CF as a "single" agent in disseminated malignancies. Some of the studies also used vincristine (VCR) but these will be specifically identified as they occur. Therapeutic programs employing other concomitant cytotoxic treatment, including radiotherapy, will not be considered. The limitations of this type of information must be emphasized since the response rate to chemotherapy is affected by variations in the definitions of patient eligibility, criteria for response, and data-reporting methods used in each trial.

RESULTS

Tables 1 and 2 detail the responses in various tumor types among 262 patients who received HDMTX-CF in published phase II trials. Unfortunately, the doses and duration of administration of HDMTX-CF were highly variable, and the number of patients treated in each disease category was relatively small. Of particular interest is the small number of patients with metastatic osteogenic sarcoma studied before making this a standard surgical adjuvant treatment. In fact, only four patients with this disease were treated strictly with HDMTX-CF, and no response was observed (table 1). Responses were observed only among patients treated with a combination of VCR and HDMTX-CF. Among the other malignancies, HDMTX-CF, with or without VCR, has shown promising results in non-Hodgkin's lymphoma, head and neck carcinoma, melanoma, and pancreatic carcinoma (table 2).

DISCUSSION

Since the high-dose regimen appears active in certain tumor types, carefully designed randomized and controlled clinical trials remain to be performed

TABLE 1.—Single-agent activity of HDMTX-CF in osteogenic sarcoma

Treatment	No. of patients	No. of responses	Investigator (ref No.)
HDMTX-CF	4	0	Pratt et al (4)
VCR + HDMTX-CF (schedule 1)	14	4	Jaffe et al (5–8) Frei et al (9)
VCR + HDMTX-CF (schedule 2)	8*	7†	Jaffe et al (8)

*Includes 4 patients with pulmonary metastases and 4 with primary tumors.

†Includes 5 complete responses evidenced by radiologic improvement and disappearance of pain.

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[2]We acknowledge the skillful assistance of Mr. William Soper and Ms. Linda Edge in the preparation of this manuscript.

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TABLE 2.—Single-agent activity of HDMTX-CF in various tumor types*

Tumor types	No. of patients	No. of responses	Ref No.
Sarcoma†,‡			
Osteogenic	26	11	4-9
Ewing's	4	1	4,10,11
Rhabdomyosarcoma	5	1	4,10
Miscellaneous	21	4	4,10,12
Total	56	17	
Lymphoma‡			
Non-Hodgkin's	30	23	12,13
Unspecified	8	4	14,15
Total	38	27	
Head and neck	37	26	12.16,17
Brain†			
Glioma	17	7	18–20
Medulloblastoma	7	4	18,19
Ependymoma	1	1	19
Total	25	12	
Breast	23	6	12
Melanoma†	22	8	21
Lung			
Small cell	8	2	12
Non-small cell	12	1	22–24
Total	20	3	
Pancreas†,‡	18	5	25
Cervix†,‡	8	3	26
Anus	4	2	27
Acute myelocytic leukemia	2	1	11

*No responses in cumulative series of ≤ 5 patients with teratoma (ref 4), acute lymphocytic leukemia (ref 11), neuroblastoma, adrenal carcinoma, and Wilms' tumor (ref 10).

†Includes patients receiving VCR prior to MTX administration.

‡Includes patients treated with escalating doses of MTX starting below 1 g/m² (25 mg/kg).

to assess the respective values of HDMTX-CF (1 g/m²/course) and conventional MTX doses not requiring CF rescue. However, the undertaking of such studies might be indefinitely delayed by a search, which perhaps would be only academic, for an optimal HDMTX-CF regimen.

The apparently successful introduction of adjuvant treatment with HDMTX-CF in osteogenic sarcoma (8) is truly remarkable in view of the limited data available in the advanced stage of the disease. These findings offer definite encouragement for future adjuvant studies in other tumors that are poorly responsive to chemotherapy.

A superiority of MTX plus VCR over MTX alone has not been established. In tumor types known to be responsive to VCR, its use precludes the evaluation of the antitumor effect of MTX. In the other tumor types, the role of VCR is unknown. VCR does increase the intracellular level of "free" MTX by retarding its exit from the cell (28), which in turn might enhance the effect of MTX on tetrahydrofolate and DNA synthesis (29, 30). However, this VCR-induced phenomenon can be observed in vitro only with certain cell lines (31, 32), suggesting that there are individual tumor thresholds for the VCR effect on the MTX transport. Thus, widespread use of the drug combination may be unwarranted in tumor types resistant to VCR, unless a VCR-induced augmentation of free intracellular MTX can be demonstrated in a specific resistant tumor line.

In summary, there are limited data on the single-agent activity of HDMTX-CF. Furthermore, interpretation of the data is obscured by the variability in the dose schedule of MTX and CF, and by the frequent inclusion of VCR in these regimens. In view of the cost and potential hazards of this therapy, additional dose-response data must be obtained before routine use of HDMTX-CF can be advocated in the advanced stage of any tumor type.

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Chemotherapy for Metastatic Osteosarcoma—Studies by the M. D. Anderson Hospital and the Southwest Oncology Group [1]

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Despite advances in the adjuvant chemotherapy for osteosarcoma, advanced, metastatic osteosarcoma in the adult remains a very difficult tumor to treat with chemotherapy. In a series of sequential studies at the M. D. Anderson Hospital and in the Southwest Oncology Group, we have concentrated on the use of adriamycin alone and in combination. We have thus far avoided the use of high-dose methotrexate because of the increased risk of toxicity in older patients with disseminated disease and because of the small number of patients with osteosarcoma treated with high-dose methotrexate who can be evaluated objectively for response. The background data on adriamycin as a single drug show a 22% objective response rate among 81 patients reviewed by Gottlieb (1). In our initial study with adriamycin as a single agent, three partial remissions and no complete remissions were seen among 11 patients treated, for a response rate of 27%. With the addition of DTIC with or without vincristine in the so-called ADIC (adriamycin and DTIC) and VADIC (vincristine, adriamycin, and DTIC) regimens, there were three complete remissions and 13 partial remissions among 46 patients for a response rate of 35% (2). More importantly, the quality of remission was substantially improved by the addition of DTIC as we have seen in the more responsive soft tissue sarcomas (3,4). Median survival for the osteosarcoma patients treated with adriamycin alone was only 3 months compared with 9 months for the patients receiving ADIC ($P < 0.01$). Considering only patients with an objective tumor regression, survival increased from 8 to 11 months with the addition of DTIC ($P < 0.2$), and for the complete responders receiving ADIC, survival is at least 15 months from the onset of chemotherapy.

The addition of cyclophosphamide to form the CYVADIC (cyclophosphamide, vincristine, adriamycin, and DTIC) regimen (2) has led to remission rates > 50% in patients with soft tissue sarcomas. We were disappointed, therefore, when only one of 29 patients with osteosarcomas achieved complete remission and only six achieved partial remission for an overall response rate of 24%. Replacing DTIC with actinomycin D to obtain the CYVADACT (cyclophosphamide, vincristine, adriamycin, and actinomycin D) regimen, we had equivalent results with two complete responders and three partial responders among 20 patients for an overall response rate of 25% (2,4). In the CYVADIC pilot study it was noted that most patients with osteosarcoma had the chondroblastic variant. Chondrosarcoma is considerably more refractory to adriamycin than other tumors. Of the 11 patients whose tumors were evaluated with regard to their pathologic subtypes, eight had chondroblastic osteosarcoma and only one (13%) responded. In contrast, two of the three patients with osteoblastic osteosarcoma had an objective tumor regression and one of these obtained complete remission. In contrast to the experience in earlier studies, however, response rates of 38%–40% were seen in the few patients registered with chondrosarcoma who received these cyclophosphamide-containing regimens. Perhaps a better explanation for the decreased response rate on the CYVADIC and CYVADACT regimens compared with the ADIC regimen is related to the lower adriamycin dose necessary to accommodate the myelosuppressive toxicity of cyclophosphamide. In the ADIC regimen, adriamycin is given at an initial dose of 60 mg/m², whereas in the cyclophosphamide-containing regimen, the dose of adriamycin is reduced to 50 mg/m². The steep dose-response curve of sarcomas to adriamycin has been defined in our dose-response study (2,5), confirming the original observations of Cortes et al (6) using adriamycin alone on a 3-day schedule.

Another observation in the original studies of Cortes et al was the increased response rate of

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patients whose interval from diagnosis to metastatic disease was prolonged. In our patients treated with ADIC the incidence of objective response was substantially higher for patients whose interval to metastasis was > 10 months. In this situation, eight of 11 patients (73%) responded compared with five of 22 (23%) with disease-free intervals of < 10 months ($P < 0.01$). Considering the time to metastasis by response category, the median time from diagnosis to metastasis was 4.5 months in patients with progressive disease or no change, 11 months in patients with partial response, and 22 months in patients with complete remission. The difference between these intervals was significant, with $P = 0.04$ for the complete responders and $P = 0.06$ for all responders.

One other factor which may influence response is the site of metastatic disease. There was no major variation by the site of the primary; however, regressions of metastases in the liver and lung were most frequent, regressions in other soft tissues were somewhat less frequent, and responses in the bone were distinctly unusual with only one of 12 patients having objective regression of bony disease.

An area which appears to be worthy of further study is that of sequential chemotherapy with L-asparaginase and methotrexate (7). We have treated a group of patients with a variety of sarcomas that failed to respond to CYVADIC and CYVADACT. Although the overall response rate in the group was quite low, approximately 15%, secondary remissions in these patients are distinctly unusual. In addition, of the four evaluable patients with osteosarcoma in that study, one had a good partial remission for 6 months and two others had stabilization of previously progressive disease. Since the doses of methotrexate used in these studies are usually 120–240 mg/m^2 (less than one tenth of the doses employed in the high-dose methotrexate-citrovorum factor rescue studies), this approach is worthy of further investigation.

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cis-Dichlorodiammineplatinum(II) in Advanced Osteogenic Sarcoma [1]

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SUMMARY

Eight patients with advanced metastatic osteogenic sarcoma were treated with *cis*-dichlorodiammineplatinum(II) (DDP). Prior to DDP, seven patients had amputations and all had received adjuvant adriamycin (ADR) therapy. In addition, prior to DDP, six patients had received high-dose methotrexate. There was one complete response (pulmonary metastases) and four partial responses (three metastases in the lungs and one in the bone). One additional patient, with local recurrence of osteogenic sarcoma of the mandible following initial resection and adjuvant ADR, was re-treated with surgery and DDP and is disease-free for > 3 years. The cumulative dose ranged from 300 to 660 mg/m^2. Toxicity included irreversible kidney damage in two patients, transient severe hematologic suppression in two patients, and nausea and vomiting in all patients. DDP is a new effective agent in the treatment of osteogenic sarcoma.

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cis-Dichlorodiammineplatinum(II) (DDP) is a chelated heavy metal with antitumor properties. This compound was initially isolated by Rosenberg in 1965 who noted inhibition of *Escherichia coli* replication. Antitumor properties were discovered and studies in animal models showed a wide range of responsiveness in chemically and virally induced transplantable tumor systems (1,2). In man, a wide range of antitumor activity was identified, notably against testicular carcinomas and epidermal carcinomas of the head and neck (3–7). The response seen in patients with advanced osteosarcoma with DDP at Roswell Park Memorial Institute is the basis of this report.

MATERIALS AND METHODS

There were four males and five females, from 13 to 43 years of age. All nine had histologically confirmed osteogenic sarcoma. All but one had a surgical procedure in a curative attempt as their initial treatment. All patients received adjuvant adriamycin (ADR) and six had also received high-dose methotrexate (HDMTX) prior to DDP. Four patients had also received other additional chemotherapy. All patients had advanced and clearly progressive disease before DDP was employed. In four patients, pulmonary metastases had been resected while a fifth patient had had re-resection of a locally recurrent mandibular lesion previously treated by excision and adjuvant ADR.

In addition to routine chemistries and blood cell counts, all patients had creatinine clearance determinations, chest roentgenograms, and skeletal surveys or bone scans. Audiograms and creatinine clearances were frequently obtained midway through the study.

DDP was obtained from the NCI as a white powder which was reconstituted with sterile water. It was given as a rapid iv infusion in all but the last two patients, who received a 6-hour infusion. Since most of these patients were treated early in our experience with DDP, the dose and schedules were

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varied. DDP was initially given at 20 mg/m²/day for 5 consecutive days, but later 120 mg/m²/day was given as a single injection with forced osmotic diuresis. Each dose was preceded by a 2-hour period of intensive hydration and followed by a 24-hour infusion of 3000 ml/m² of fluid. Mannitol was used in the 6-hour forced diuresis following DDP infusion towards the end of the study when higher DDP doses were employed.

Treatment was discontinued in any patient who failed to show a therapeutic response. All patients received more than one course.

A complete remission was defined as a complete disappearance of all measurable parameters of disease. A partial response was defined as a decrease in volume of all measurable disease parameters > 50%. No response was defined as < 50% regression and no visible progression. Progressive disease was defined as any increase in the size of a measurable lesion.

RESULTS

Table 1 summarizes clinical course, prior chemotherapy and surgery, and subsequent response to DDP. Table 2 illustrates the DDP dose and schedule and the response to DDP. One patient had a complete response with complete clearing of a large left pulmonary mass and pleural effusion; subsequent chest roentgenograms and tomograms remain clear for > 18 months (fig 1, a and b).

Three patients with pulmonary metastases had partial responses lasting 2–5 months, and a fourth had regression of bony metastases for 5 months

TABLE 1.—Patient characteristics and response to DDP

Patient No.	Age/sex	Primary tumor site	Surgery	Prior chemotherapy and clinical course	Response to DDP
1	14/F	Left mandible	Left mandibulectomy	Adjuvant ADR, local recurrence	NE*—disease-free > 37 mos
2	13/F	Left proximal humerus	None	ADR + HDMTX for pulmonary metastases at presentation, progressive disease	No response
3	13/M	Left distal femur	Mid-femur amputation	Adjuvant ADR but pulmonary metastases, autologous tumor cells, and isophosphamide, progressive disease	No response
4	19/M	Left distal tibia	High-thigh amputation	Adjuvant ADR but pulmonary metastases and cyclophosphamide, no response	Partial response—> 75% shrinkage of skull metastases
5	15/M	Left distal femur	Initial tumor resection and bone graft; left hip disarticulation 3 wks later	Adjuvant ADR but pulmonary metastases	No response
6	22/M	Left distal femur	Mid-femur amputation	Adjuvant HDMTX, ADR, and vincristine but pulmonary metastases and cyclophosphamide, no response	Partial response—> 50% shrinkage of pulmonary metastases
7	14/F	Left proximal tibia	High-femur amputation	Adjuvant ADR + HDMTX but pulmonary metastases	Partial response—> 50% shrinkage of pulmonary metastases
8	18/F	Right distal femur	High-femur amputation	Adjuvant ADR but pulmonary metastases	Complete response—complete clearance of pulmonary metastases
9	43/F	Left femur	Left hip disarticulation	Pulmonary metastases 20 mos after surgery; cyclophosphamide, vincristine, ADR, and HDMTX, no response	Partial response—> 50% shrinkage of pulmonary metastases

*NE = not evaluable for objective response.

(partial response). The girl (who had a local recurrence in the mandible after subtotal mandibular resection and 10 months of adjuvant ADR therapy, subsequently underwent further resection, and then received 320 mg/m² of DDP over a 4-month period) is currently disease-free > 37 months later.

TOXICITY

Toxicity reported with DDP has generally fallen into five categories: renal, audiologic, hematopoietic, gastrointestinal, and hepatic (8–10) (*see* table 3 for definition of toxicity).

Renal toxicity was severe in two patients and appeared to be irreversible in one of these. Moderate but irreversible nephrotoxicity was seen in one patient; mild to moderate reversible toxicity occurred in two others. Auditory loss was mild in two patients. There were five instances of mild and two instances of severe hematologic toxicity, but these were clinically significant in only one patient who required hospitalization for presumed sepsis during a period of neutropenia. All patients experienced

TABLE 2.—DDP dosage and clinical response

Patient No.	DDP dose/schedule	Cumulative dose	Clinical response to DDP
1	20 mg/m²/day × 4 days/mo × 4 courses	480 mg 320 mg/m²	NE*—DDP in conjunction with repeat surgery given over 4 mos; now disease-free > 37 mos
2	20 mg/m²/day × 5 days q4wks × 3 courses	450 mg 320 mg/m²	No response—continued progression with pulmonary metastases and enlarging primary and multiple new bone metastases; received cyclophosphamide; died
3	20 mg/m²/day × 5 days × 3 courses	325 mg 300 mg/m²	No response—progressive pulmonary metastases; bone marrow and liver metastases; died
4	30 mg/m²/day × 4 days q4wks × 3 courses 30 mg/m²/day × 2 days q2wks × 1 course 20 mg/m²/day × 4 days × 1 course	684 mg 498 mg/m²	Partial response—pulmonary stabilization × 5 mos; skull metastases decreased > 75% after 1st course; subsequent pulmonary bony progression and brain metastases; DDP discontinued and patient received HDMTX without effect; died (duration of response, 5 mos)
5	65 mg/m² q4days × 1 course 115 mg/m²/day × 1 course	545 mg 300 mg/m²	No response—3 wks after DDP new lung metastases appeared
6	35 mg/m² q12hrs × 2 doses twice weekly × 3½ wks 50 mg/m² q12hrs × 2 doses twice weekly × 1 wk	840 mg 336 mg/m²	Partial response—initial increase in size of pulmonary metastases; drug dosage increased with subsequent 50% shrinkage × 2 mos; thoracotomy with multiple wedge resections when metastases then increased in size (duration of response, 2 mos); receiving mitomycin C and still alive
7	25 mg/m²/day × 4 days × 1 course 40 mg/m²/day × 2 days q3wks × 2 courses 50 mg/m²/day × 2 days q4wks × 4 courses	996 mg 664 mg/m²	Partial response—50% shrinkage of large left pulmonary metastasis with complete disappearance of 2 others within 5 mos; 1 mo later, multiple new metastases on right lung associated with bone metastases; chemotherapy discontinued with increased size and No. of pulmonary metastases and bone pain (duration of response, 5 mos)
8	50 mg/m²/day × 3 days q3wks × 1 course 50 mg/m²/day × 2 days q3wks × 1 course 60 mg/m²/day × 2 days q3wks × 1 course†	580 mg 386 mg/m²	Complete response—almost complete clearing of left chest (> 75%) on roentgenogram 3 wks after DDP; tomograms at 8 wks showed probable left pleural metastases; later complete clearing on roentgenogram and tomograms > 18 mos
9	120 mg/m²/day q3–4wks × 2 courses 35 mg/m²/day q3–4wks × 2 courses	488 mg 305 mg/m²	Partial response—> 50% decrease in size of large left pulmonary metastases; pulmonary lesions stable × 4 mos after initial shrinkage (duration of response, > 4 mos)

*NE = not evaluable for objective response.
†Slow infusion.

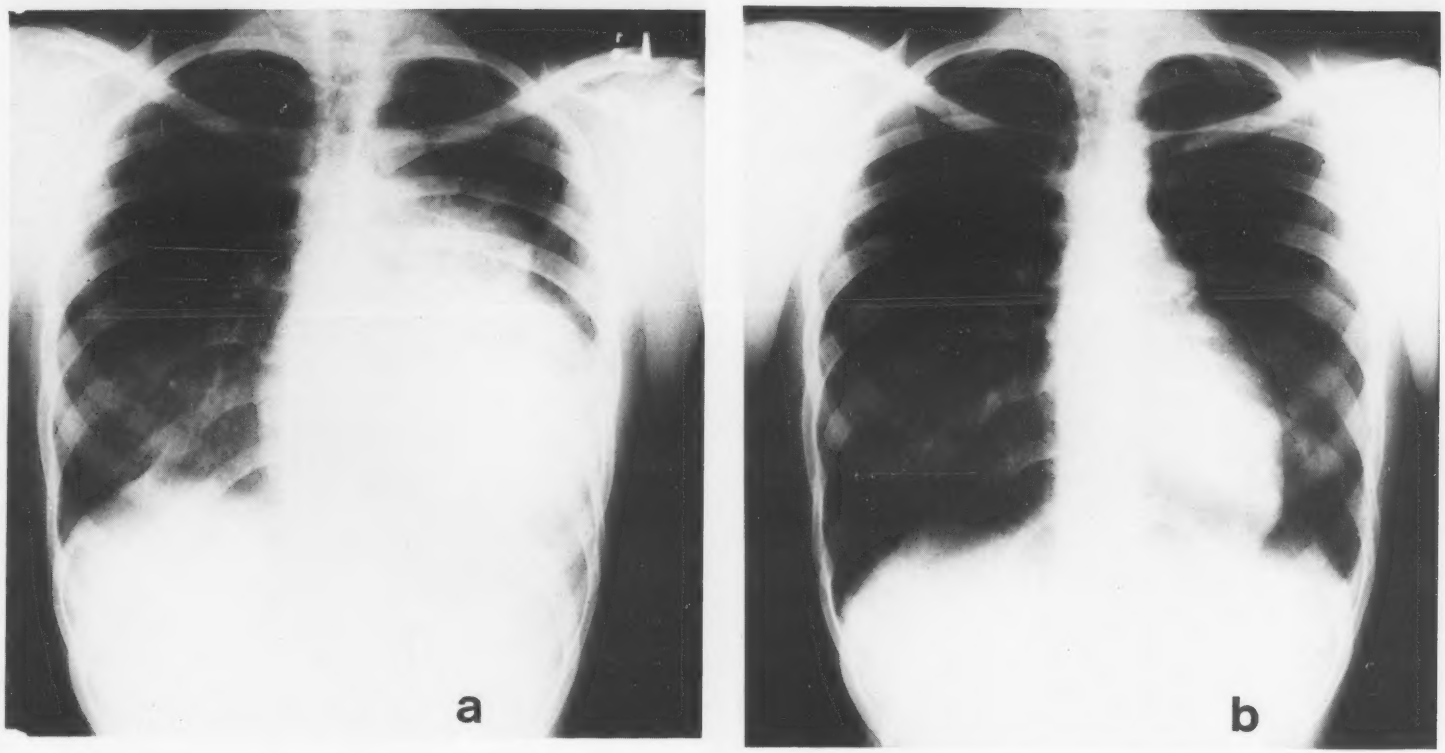

FIGURE 1.—a. Chest roentgenogram of patient 8 at time of initial presentation of pulmonary and pleural metastases. b. Chest roentgenogram of same patient 2 mos later after 3 courses of DDP shows complete clearing.

nausea and vomiting. Liver toxicity was moderate in one patient.

DISCUSSION

The mechanism of action of DDP is similar to the action of a bifunctional alkylating agent and binds preferentially, but not exclusively, to guanine (11–15). Rosenberg (13) also postulates that DDP enhances the antigenicity to the tumor system. At low concentrations in vitro, DDP selectively inhibits RNA and protein synthesis.

DDP is most effective when given iv and is widely distributed with < 10% of the DDP remaining in the plasma 1 hour after administration (16). It is first concentrated in the kidneys and then in the liver (17). Clearance is biphasic with an initial half-life of 30–50 minutes and a second half-life of from 2 to 5 days (5). It has a low therapeutic index (18). The drug is excreted in the urine.

In five of eight patients objective tumor shrinkage was noted; this included one complete response in a young woman with a large left pulmonary metastasis and a pleural effusion. In our hands, DDP appears at least as good as ADR or HDMTX in advanced osteogenic sarcoma.

Renal toxicity has been the major dose-limiting problem with the use of DDP (1,19); it is cumulative, but usually initially reversible. Toxicity has been initially manifested by decreasing creatinine clear-

TABLE 3.—Toxicity

Patient No.	Cumulative dose	Toxicity*				
		Renal	Auditory	Hematologic	Gastrointestinal	Hepatic
1	840 mg 336 mg/m²	None (no creatinine clearance)	Not tested	None	Mild	None
2	450 mg 320 mg/m²	None (no creatinine clearance)	Not tested	Severe	Mild	None
3	325 mg 300 mg/m²	Mild	Not tested	Mild	Mild	None
4	684 mg 498 mg/m²	Mild	Not tested	Mild	Moderate	None
5	545 mg 300 mg/m²	Severe	Not tested	Mild	Mild	Mild
6	840 mg 336 mg/m²	None	None	Severe	Mild	None
7	996 mg 664 mg/m²	Moderate†	Not tested	None	Severe	Moderate
8	580 mg 386 mg/m²	None	Mild; high-frequency loss at 1st infusion	Mild	Moderate	None
9	488 mg 305 mg/m²	Severe†	Mild	Mild	Moderate	None

*Definitions of toxicity:

Toxicity	Degree		
	Mild	Moderate	Severe
Renal			
BUN (mg/100 ml)	25–35	36–50	> 50
Serum creatinine (mg/100 ml)	1.3–2.0	2.1–2.5	> 2.5
Creatinine clearance (ml/min)	75–90	60–75	< 60
Auditory (decibel loss)	10–50	50–100	> 100
Hematologic			
Hemoglobin (g/100 ml)	10–12	7–10	< 7
Wbc count (cells/mm³)	2500–3500	1500–2500	< 1500
Platelet count (cells/mm³)	75,000–100,000	50,000–75,000	< 50,000
Gastrointestinal			
Nausea and vomiting	No antiemetics required	Antiemetics required	Not controlled by antiemetics
Hepatic			
SGOT (mg/100 ml)	45–100	100–300	300

† Irreversible.

ances followed by elevated BUN and creatinine and by proteinuria. The pathogenesis appears to be acute tubular necrosis similar to kidney damage induced by heavy metal poisoning (1). In this study, two patients had irreversible kidney damage. One of these patients had had prior nephrotoxicity with MTX evidenced by a reduction of creatinine clearance to 33 ml/minute which subsequently returned to normal. It was noted that this patient's creatinine clearance decreased to 30 ml/minute after her first course of DDP, but that two subsequent courses of DDP at lower doses with slow infusion and forced diuresis produced no further worsening of kidney function. The other patient with irreversible kidney damage received the highest cumulative dosage of DDP in this study, greater than twice the amount received by most other patients in the study. Currently, it appears that slow infusion with forced diuresis is less nephrotoxic and will allow increased amounts of DDP to be given with the same clinical efficacy (19).[5,6]

The other significant irreversible toxicity that has been reported has been bilateral ototoxicity which progresses from higher to lower frequencies. Initially, this is not recognized by the patients, but is detected by serial audiograms; in several studies, hearing loss only occurred at cumulative doses which exceeded 4.0 mg/kg (4). Two patients in this series showed mild high-frequency loss.

In our study, as in others, gastrointestinal symptoms of anorexia and nausea and vomiting occurred in all patients to varying degrees, but these were generally controllable. Animal studies have shown enterocolitis histologically (19). In one patient whose nausea and vomiting was not controlled by antiemetics, a strong psychologic overlay was present.

Bone marrow suppression occurred, but was usually not severe. Hemoglobin levels remained generally stable and wbc and platelet counts rarely fell to < 2000 and 100,000/mm^3 respectively. The nadir has occurred between 14 and 21 days. In our study, two patients had severe hematologic depression, one requiring hospitalization for possible sepsis. Both of these patients recovered.

Transient hepatotoxicity with transaminase elevation has also been mentioned in several studies (5). In the present study, the one patient who had moderate elevation of liver enzymes prior to DDP showed no further increase with drug.

Allergic and anaphylactic reactions have been reported, but no instance of this has occurred in any patient during this study.

DDP and ADR have been used in combination in studies of patients with advanced solid tumors (20–22). No potentiation of toxicity occurred and it has been suggested that this combination is synergistic. This combination appears very attractive in osteogenic sarcoma since ADR is also an effective agent in this cancer and the primary toxic effects do not overlap (ie, bone marrow depression and cardiotoxicity from ADR and renal and auditory toxicity from DDP).

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Sequential Combination Chemotherapy (Containing High-Dose Cyclophosphamide) for Metastatic Osteogenic Sarcoma

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SUMMARY

Eleven patients with metastatic osteogenic sarcoma were treated with cyclophosphamide, adriamycin, and, in some cases, high-dose methotrexate. In the event of metastatic progression, the dose of cyclophosphamide was escalated by increasing the number of consecutive daily infusions (dose, 45 mg/kg/day). The results indicate that metastatic osteogenic sarcoma is marginally responsive to adriamycin and cyclophosphamide but rarely responsive to high-dose methotrexate as administered in this trial. The response of metastatic lesions was not improved by escalating the dose of cyclophosphamide.

[Cancer Treat Rep 62:247–250, 1978]

Adjuvant chemotherapeutic regimens appear to have achieved some success in preventing or at least delaying the overt metastases of osteogenic sarcoma (*see* related papers in this issue). Little progress, however, has been made in the treatment of established metastatic disease (1,2). Approximately 20%–25% of the patients who develop a solitary pulmonary nodule and who undergo complete surgical resection of that lesion may survive for ≥ 5 years following thoracotomy (3). However, $< 10\%$ of the patients with pulmonary metastases have solitary nodules. Of those patients with multiple lesions, very few have surgically resectable disease, and of those patients who do undergo complete resection of multiple metastases, $< 10\%$ survive for 5 years (4,5).

Chemotherapy for overt metastatic disease has been even less effective than surgical resection in prolonging life. Cyclophosphamide, adriamycin, and methotrexate are among the drugs that may induce temporary responses (6). However, long-term survival following chemotherapy for metastatic osteogenic sarcoma is exceedingly rare. The clinical trial which forms the basis of this report was designed to test the hypothesis that very high doses of cyclophosphamide in combination with adriamycin, and in certain patients, high-dose methotrexate, might have greater tumoricidal efficacy in metastatic osteogenic sarcoma than has been the case with regimens containing conventional doses of cyclophosphamide. There is evidence in the treatment of some other human tumors (multiple myeloma and lung and ovarian carcinomas) that high-dose alkylating-agent therapy is more effective than low-dose therapy (7–9). The plan of this trial (protocol No. 75-3) was to escalate sequentially the dose of cyclophosphamide, used in combination with the other agent(s), in the event of metastatic progression.

PATIENTS AND METHODS

Two groups of patients were treated following roentgenographic evidence (and in some cases, biopsy confirmation) of multiple overt metastases. Group I consists of patients presenting with metastases at the time of initial diagnosis who had received no previous chemotherapy or, at most, one dose of adjuvant methotrexate. Group II comprises patients who had developed metastases while receiving adjuvant methotrexate. Two patients underwent total resection of pulmonary metastases prior to entry in this trial, but in the remainder the metastases were not considered resectable initially.

Initial treatment for group I patients consisted of two cycles of adriamycin (A) and cyclophosphamide

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(C), separated by a rest interval to permit bone marrow recovery. Each cycle consisted of adriamycin (35 mg/m²/day iv for 2 consecutive days) plus cyclophosphamide (45 mg/kg/day iv on the first day) (AAC). AAC was then followed by two cycles of high-dose methotrexate (250 mg/kg iv over 6 hours) with citrovorum factor rescue. For group II patients, already methotrexate failures, initial treatment consisted of AAC followed by AACC (adriamycin and cyclophosphamide, each given on 2 consecutive days), and finally a course of cyclophosphamide (25 mg/kg/dose) administered every other day for five doses (CCCCC). In general, both groups of patients were initially treated for approximately 10 weeks. At the conclusion of this phase, all patients were re-evaluated. Thoracotomy was performed in patients then considered to have surgically resectable metastases. For patients who were rendered clinically free of tumor following thoracotomy or initial chemotherapy, or for patients whose metastatic lesions had shown no increase in size during the initial phase of treatment, maintenance therapy consisting of methotrexate and/or AAC was administered to group I and AAC and/or CCCCC to group II. The choice of a maintenance regimen in both groups was based on the regimen which appeared to have been most effective during the initial phase.

A second phase was initiated for patients in groups I and II whose metastatic lesions progressed during the initial phase of this trial. All patients entering this second phase were given cycles of chemotherapy consisting of AA (adriamycin on 2 consecutive days) plus 2, 3, and finally 4 consecutive days of cyclophosphamide (45 mg/kg/day). Patients rendered free of tumor at the conclusion of the second phase received maintenance chemotherapy with intermittent cycles of AACC. All patients achieving a total adriamycin dose of approximately 550 mg/m² received maintenance chemotherapy with high-dose cyclophosphamide alone. Chest roentgenogram, tomography, metastatic survey, and radio-isotopic scanning were performed prior to each cycle of chemotherapy.

Response Criteria

Complete response is defined as the disappearance of all clinically detectable tumor. Partial response is defined as a decrease in a clearly measurable lesion by $\geq 50\%$ of the product of the longest perpendicular diameters. Improved (minor response) is defined as a decrease in a clearly measurable lesion by $\geq 25\%$ of the product of the longest perpendicular diameters. Progressive disease is defined as the occurrence of any new lesion or $\geq 25\%$ increase in the product of the longest perpendicular diameters of a measurable lesion. Stable disease is defined as a lack of response or progression for 3 weeks.

RESULTS

Eleven patients (nine males and two females) were enrolled in this trial. The age range was 11–20 years with a median of 15 years. All patients had osteogenic sarcoma of the lower extremity (six femur, five tibia). Ten patients had undergone initial amputation of the extremity bearing the tumor. One patient received radiation therapy (6000 rads) to the primary lesion. Overt metastases presented as pulmonary lesions in ten of the 11 patients, and as a lesion in the scapula in one (followed by pulmonary metastases). Six of the 11 patients were in group I of this study (metastases at the time of initial diagnosis) and five were in group II (recurrence following methotrexate adjuvant therapy).

Only two patients responded to the chemotherapy. One of these patients (group II) achieved a complete remission of his metastases during maintenance consisting of AAC alternating with CCCCC. His lesions had been stable on completion of the initial phase of treatment. The second responsive patient (also group II) improved transiently (6 weeks) following AACC given as a part of the second phase of therapy. He showed no further improvement with escalation of cyclophosphamide. One patient (group I), whose primary lesion had been treated initially with radiotherapy, showed stabilization of his metastatic lesions following initial treatment. The primary tumor was eventually treated by amputation following local recurrence, but metastases remained stable with chemotherapy until death occurred. Of the 11 patients entered in this study, only one proceeded through both treatment phases in their entirety.

The responses to the various cycles employed in this trial are summarized in table 1. Of 22 courses of AAC, none was associated with improvement in metastatic lesions, although 15 of the courses resulted in stabilization of metastases. Four of 18 courses of AACC were effective in reducing the size of metastatic lesions in two patients, but further consecutive doses of cyclophosphamide beyond AACC did not produce a significant benefit in any patient. Following all seven courses of AACCC or AACCCC, progressive metastatic lesions were observed. Of 12 courses of alternate-day cyclophosphamide (CCCCC), two courses in one patient were associated with improvement of pulmonary metastases, but no patient demonstrated improvement following methotrexate.

TABLE 1.—Antitumor efficacy of various treatment cycles of Pediatric Oncology Branch protocol No. 75–3

Treatment cycle	Disease status/ No. of patients
AAC (22 courses)	Improved/0 Stable/15 Progressive/6 Not evaluable/1
AACC (18 courses)	Improved/4 Stable/7 Progressive/5 Not evaluable/2
AACCC (4 courses)	Improved/0 Stable/1 Progressive/3
AACCCC (3 courses)	Improved/0 Stable/0 Progressive/3
CCCCC (12 courses)	Improved/2 Stable/6 Progressive/4
Methotrexate (33 courses)	Improved/0 Stable/15 Progressive/18

Of 11 patients enrolled in this trial, seven died at 4, 9, 12, 12, 13, 14, and 18 months after the initial diagnosis of osteogenic sarcoma. Of these seven deaths, four were associated with progressive metastatic disease, two were associated with septicemia in the presence of stable or progressive metastatic disease, and one was associated with acute gastrointestinal hemorrhage secondary to the effects of chemotherapy. Four of the 11 patients studied are alive at 7+, 7+, 12+, and 14+ months following diagnosis.

Toxicity associated with this clinical trial is described in table 2. Twenty-two courses of AAC were associated with only one complication (gastrointestinal hemorrhage plus *Clostridium* sepsis). However, the majority of patients receiving courses of AACC required hospitalization for fever in the presence of granulocytopenia, and two episodes of fatal septicemia occurred in this setting. Of four courses of AACCCC, one resulted in a nonfatal septicemia. The CCCCC regimen was well tolerated, with only one of ten courses requiring patient hospitalization for fever in the presence of granulocytopenia. None of the courses of methotrexate was associated with a complication. Cardiac toxicity due to adriamycin was observed in one patient.

DISCUSSION

The objectives of this clinical trial were (*a*) to confirm the responsiveness of metastatic osteogenic sarcoma to adriamycin, cyclophosphamide, and methotrexate (6); (*b*) to learn if responsiveness could be improved by increasing the dose of cyclophosphamide; and (*c*) to assess the toxicity of these agents when given in escalating doses. The results of this trial revealed only one complete and durable response of metastatic osteogenic sarcoma to chemotherapy alone; additionally, two patients demonstrated partial and transient shrinkage of their metastatic lesions with escalation of the dose of cyclophosphamide. About half of the patients enrolled in this protocol showed some periods of stabilization in the size of their metastases.

The results of the protocol are disappointing, and it is noteworthy that the only patient who achieved a complete remission did so without proceeding through the second phase of treatment. Escalating doses of cyclophosphamide do not appear to be warranted in view of the increased toxicity and modest number of responses achieved with the regimen. Recent observations suggest that rather than escalating the doses of alkylating agents as tumor size progresses, a more rational approach may be to offer initial high-dose chemotherapy following total surgical resection of metastatic lesions. Such a strategy would exploit the possibilities that the rate of regression is shallow when the tumor burden is small (10), that cell kill increases with increasing doses of alkylating agents, and that a small tumor burden will be more readily eliminated than a large tumor burden with high-dose treatment (11).

TABLE 2.—Toxicity associated with various cycles of Pediatric Oncology Branch protocol No. 75–3

Treatment cycle	Results
AAC (22 courses)	1 death from hemorrhagic gastroduodenitis and *Clostridium* sepsis.
AACC (18 courses)	Wbcs < 1000/mm^3 in 13 patients for median of 5 days. Fever in 13 patients for median of 6 days. 3 patients with proven sepsis, 2 fatal.
AACCC (4 courses)	Wbcs < 1000/mm^3 in 4 patients for median of 5 days. Fever in 4 patients for median of 5 days. 1 patient with proven sepsis, non-fatal.
AACCCC (3 courses)	Wbcs < 1000/mm^3 in 3 patients for median of 14 days. Fever in 3 patients for median of 8 days. 1 patient with proven sepsis, non-fatal.
CCCCC (12 courses)	Wbcs < 1000/mm^3 in 1 patient for 5 days. Fever in 1 patient for 5 days.
Methotrexate (33 courses)	No complications.

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Combination Chemotherapy for Osteosarcoma [1]

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SUMMARY

Because of the great risk for development of pulmonary metastases following amputation for osteosarcoma, 24 consecutive patients with "clinically localized" osteosarcoma of an extremity were given adjuvant combination chemotherapy with adriamycin-cyclophosphamide-high-dose methotrexate-citrovorum factor. Thirteen of these patients remain free of tumor from 11 to 48 months following amputation. The median disease-free survival is estimated to be 18 months and the median survival 27 months. No relapses have been observed in any patients surviving free of disease beyond 23 months. Combination chemotherapy was also given to 16 patients whose disease was not localized; eight with pulmonary metastases at or following diagnosis, one with nodal metastases at diagnosis, two with osteosarcoma following radiation therapy for other malignant tumors, three with osteosarcoma of flat bones, one with parosteal osteosarcoma, and one with multifocal osteosarcoma. Three of this latter group of patients are surviving free of tumor at 8, 17, and 19 months from diagnosis. Two young patients died from complications of methotrexate and adriamycin toxicity.

[Cancer Treat Rep 62:251–257, 1978]

Since 1972, considerable interest has developed in the treatment of children with osteosarcoma. Following the report by Jaffe (1) on the response of metastatic osteosarcoma following treatment with high-dose methotrexate-citrovorum factor rescue, and the report of Cortes et al (2) on similar responses after treatment with adriamycin, many oncology centers have developed adjuvant chemotherapy programs for patients with osteosarcoma in an attempt to prevent pulmonary or bony metastases (3–9).

This paper reports our experience with 41 consecutive patients with osteosarcoma treated with combination chemotherapy between December 1972 and December 1976.

PATIENTS AND METHODS

Twenty-four consecutive patients with "clinically localized" osteosarcoma of an extremity were admitted to a planned protocol study in which they received adjuvant chemotherapy following amputation (table 1). None of these patients had evidence of pulmonary or bony metastases at the time of admission to the study. Fourteen patients had lesions of the femur, five of the tibia, three of the humerus, one of the fibula, and one of the metatarsal. Transosseous amputations were performed for 20 of these 24 patients; hemipelvectomy, forequarter amputation, and scapulohumeral disarticulation were performed for the additional four patients.

Chemotherapy was administered following satisfactory postoperative recovery (9). Adriamycin, 25 mg/m^2, was given iv on Days 1 and 2 of each monthly treatment period and was followed by cyclophosphamide, 600 mg/m^2, on the third day. Approximately 2 weeks following the administration of these agents, patients were admitted for methotrexate, 100 mg/kg by iv infusion over a 6-hour period, followed in 3 hours by citrovorum factor, 5 mg/kg iv in eight divided doses administered at 3-hour intervals. The citrovorum factor administration was continued to 72 hours (12 mg/m^2 im at 6-hour intervals). The dose of methotrexate was not increased to > 100 mg/kg for these patients. After

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TABLE 1.—"Clinically localized" osteosarcoma: disease-free survival after amputation and adriamycin-cyclophosphamide-high-dose methotrexate-citrovorum factor

Patient No.	Age/sex	Primary tumor site	No. of chemotherapy courses	Disease-free survival (mos)	Survival (mos)
1	14/M	Femur	10	48+	48+
2	15/M	Femur	10	46+	46+
3	18/M	Femur	10	45+	45+
4	13/M	Tibia	10	13*	18
5	10/F	Femur	10	22*	26
6	16/F	Femur	3	3†	3
7	13/F	Femur	10	12*	19
8	14/M	Tibia	9	10‡	27
9	6/F	Femur	10	33+	33+
10	15/F	Femur	10	13‡	31+
11	11/M	Femur, neck	10	32+	38+
12	17/M	Humerus	10	11‡	22
13	16/M	Femur	10	6‡	16
14	14/M	Humerus	8	10‡	25
15	14/M	Humerus	10	27+	27+
16	13/M	Femur	10	25+	25+
17	8/F	Femur	10	23+	23+
18	17/M	Fibula	6§	23+	23+
19	17/M	Tibia	6§	21+	21+
20	28/M	Tibia	10	21+	21+
21	16/M	Metatarsal	10	18+	18+
22	11/F	Femur	6	9‡	15
23	10/F	Femur	5	5‡	7
24	13/F	Tibia	10	11+	11+

* Metastases detected after chemotherapy.
† Died on Day 17 after 3rd high-dose methotrexate-citrovorum factor course.
‡ Metastases detected while receiving chemotherapy.
§ Refused further chemotherapy.

March 1974, iv hydration was administered before and after methotrexate infusions. The planned chemotherapy program required that patients receive ten monthly cycles of adriamycin-cyclophosphamide-methotrexate-citrovorum factor. Therefore, the minimum treatment time would be 10 months' duration, one standard deviation beyond the median time (5 months) to diagnosis of metastatic disease in our previously evaluated patients with osteosarcoma of an extremity.

During the same time, 16 additional patients presented for treatment of nonlocalized or nonextremity osteosarcoma. Since these patients did not qualify as patients having clinically localized osteosarcoma, their management was individualized to best treat the special clinical conditions which they presented. Generally, they received similar chemotherapy; however, the dose of methotrexate was increased from 100 mg/kg following initial failure of response. These increased doses of methotrexate ranged from 200 to 300 mg/kg which on occasion were delivered at weekly intervals. The clinical situations represented by these 16 patients are outlined in table 2. As shown in this table, certain additional complicating factors required unique considerations for the treatment of these patients. For example, three patients were pregnant at the time of their diagnosis (10), two patients were < 6 years old at the time of treatment (11), and one patient had the additional complicating feature of Down's syndrome.

RESULTS

Adjuvant Chemotherapy for "Clinically Localized" Osteosarcoma of an Extremity

Pertinent characteristics of these 24 patients including number of courses of chemotherapy, disease-free interval, and survival following amputation are shown in table 1. Survival and disease-free survival curves are depicted in figure 1. The median survival time is estimated to be 27 months and the median disease-free survival 18 months. As of January 1977, none of the nine patients who have survived free of disease for ≥ 23 months have relapsed or died.

Thirteen patients remain free of pulmonary and bony metastases from 12 to 48 months, having received six to ten courses of chemotherapy as outlined. Patients 18 and 19 refused further chemotherapy following completion of six chemotherapy

TABLE 2.—Osteosarcoma patients with special clinical conditions treated with adriamycin-cyclophosphamide-high-dose methotrexate-citrovorum factor

Category	Patient No.	Age/sex	Disease site	Comments	No. of chemotherapy courses	Response after chemotherapy	Outcome
A. Osteosarcoma of long bone with pulmonary metastases at diagnosis	1	17/M	Distal radius	Amputation, midhumerus	6	Complete disappearance of pulmonary metastases for 4 mos	Died of disease, 16 mos
	2	20/M	Distal femur	Subtrochanteric amputation	3	No response	Died of disease, 4 mos
	3	16/F	Distal tibia	Below-the-knee amputation, resection of pulmonary metastases	7	Recurrence of pulmonary metastases at 8 mos	Died of disease, 12 mos
	4	9/F	Midfemur	Hip disarticulation, multiple large metastases	3	No response	Died of disease, 7 mos
	5	7/F	Distal femur	Hip disarticulation	6	Partial response	Died of disease, 15 mos
B. Osteosarcoma of long bone with pulmonary metastases following amputation	1	19/F	Distal femur	Pulmonary and bony metastases 9 mos after amputation; pregnant at time of diagnosis	11	Clearing of pulmonary metastases, regression of rib metastases for 10 mos	Died of disease, 25 mos
	2	15/M	Distal femur	Single central pulmonary metastases excised 14 mos after amputation	6	No measurable tumor after resection	No evidence of disease, 19+ mos from pulmonary resection
	3	16/F	Proximal humerus	Pregnant at time of forequarter amputation	10	Disappearance of pulmonary metastases and cervical node metastasis for 5 mos	Died of disease, 17 mos
C. Osteosarcoma of long bone, nodal metastases	1	5/M	Distal femur	Down's syndrome, femoral and iliac node metastases	2	No response	Died of septicemia following methotrexate toxicity 2 mos from diagnosis
D. Osteosarcoma following radiotherapy	1	13/F	Zygoma, left	Bilateral retinoblastoma; 7000 rads delivered to left orbit 14 yrs before development of osteosarcoma	3	No response	Died of disease, 4 mos
	2	25/F	Clavicle	Hodgkin's disease stage IIB; 3500 rads delivered to mantle ports 8 yrs prior to development of osteosarcoma; incomplete resection of osteosarcoma	10	No recurrence	No evidence of disease, 17+ mos

TABLE 2.—Osteosarcoma patients with special clinical conditions treated with adriamycin-cyclophosphamide-high-dose methotrexate-citrovorum factor—Continued

Category	Patient No.	Age/sex	Disease site	Comments	No. of chemotherapy courses	Response after chemotherapy	Outcome
E. Osteosarcoma of flat bone	1	9/F	Scapula	Invasion of chest wall	2	No response	Died of disease, 8 mos
	2	24/F	Mandible	Partial resection; pregnant at time of diagnosis	4	Local recurrence at 4 mos	Died of disease, 10 mos
	3	4/M	Orbit, roof	Incomplete resection	5	No measurable tumor, no recurrence	Died of adriamycin cardiotoxicity 7 mos from diagnosis; cumulative dose, 280 mg/m²
F. Parosteal osteosarcoma	1	17/M	Midfemur	Hip disarticulation	6	No recurrence	No evidence of disease, 8+ mos
G. Multifocal osteosarcoma	1	11/F	Distal femur	Bilateral retinoblastoma diagnosed at age 6 mos; other primary tumors in both tibiae, humeri	6	Progression of bony tumors; pulmonary metastases at 6 mos from diagnosis	Living with disease, 11+ mos

cycles. Sixteen patients completed the planned ten cycles of chemotherapy within 13 months, and 13 have received no additional therapy for 1–36 months. None of the 24 patients developed local recurrence.

Seven patients (Nos. 8, 10, 12–14, 22, and 23) developed metastases while receiving chemotherapy from 6 to 13 months following diagnosis. Six of these patients had pulmonary metastases, and one had bony and pulmonary metastases (No. 22). Pulmonary metastases were unilateral in three of these patients.

Three patients (Nos. 4, 5, and 7) developed metastases 2, 2, and 10 months after completion of the ten courses of chemotherapy. Two of these patients had pulmonary metastases only, while the third had bony and pulmonary metastases. Pulmonary metastases for each of these patients were unilateral.

Surgical removal of pulmonary metastases was attempted for seven patients (12). Only one of these seven patients is surviving; he remains free of tumor 17 months following thoracotomy and wedge resections of five metastases, administration of increased doses of methotrexate (200 mg/kg), and influenza virus-infected tumor cell vaccine for 1 year (13).

One patient (No. 6) died 17 days after her third infusion of methotrexate. Methotrexate toxicity was characterized by exfoliative dermatitis, severe pancytopenia, hepatic and renal failure, and *Escherichia coli* and *Candida tropicalis* septicemia. No evidence of tumor was found at autopsy (14).

The other toxic effects encountered in most of these patients have previously been reported (9). Clinical toxic effects included nausea, vomiting, abdominal discomfort, alopecia, hyperpigmentation of dermal creases, acne, exfoliative skin changes, and infections. Laboratory evidence of toxic manifestations included anemia, leukopenia, megaloblastic changes of the bone marrow, transient elevations of the SGOT and LDH isozyme levels, transient elevations in serum uric acid and BUN levels, and transient minor coagulation abnormalities. Abnormalities of creatinine clearance did not develop during or following treatment with these agents.

Chemotherapy for Osteosarcoma Patients With Special Clinical Conditions

Measurable responses were documented for two of five patients with osteosarcoma of the long bones with pulmonary metastases at the time of diagnosis.

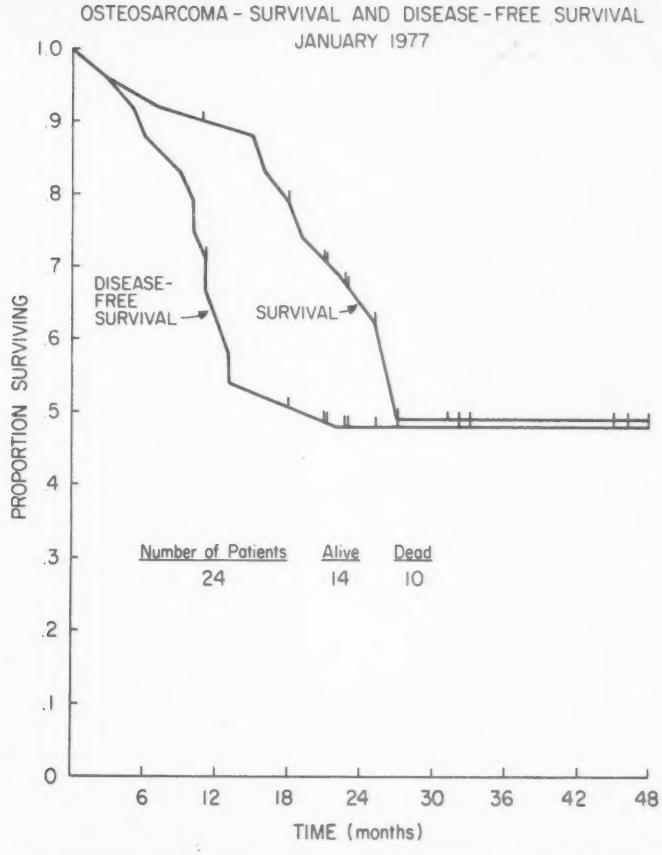

FIGURE 1.—Estimated survival and disease-free survival by life-table technique after amputation and adjuvant adriamycin-cyclophosphamide-high-dose methotrexate-citrovorum factor for osteosarcoma.

These five patients died from the effects of pulmonary metastases from 4 to 16 months after diagnosis.

Three patients with osteosarcoma of the long bones were referred for treatment following amputation and development of pulmonary metastases. Two of these patients were pregnant at the time of their amputations. These patients developed responses following chemotherapy, but died of tumor 17 and 25 months following diagnosis (10). The third patient is surviving free of tumor 33 months from diagnosis, 19 months following resection of a single central pulmonary metastasis.

A 5-year-old boy with Down's syndrome had femoral and iliac node metastases associated with primary osteosarcoma of the distal femur. He had toxic reactions following a second high-dose methotrexate infusion (100 mg/kg) and died with *Pseudomonas* septicemia 19 days following the methotrexate treatment. At post-mortem examination, active tumor was found in the femur, thigh, and pelvis. Delay in the excretion of methotrexate and excessive emesis were associated with this patient's development of profound toxic reactions.

Two patients were treated following the development of radiation-associated osteosarcoma. No response was observed for one of these patients whose initial diagnosis was retinoblastoma. The other patient, originally treated for Hodgkin's disease, had an incomplete resection of the tumor of the clavicle; she remains free of evident tumor 17 months following the initial treatment of osteosarcoma.

Three patients with osteosarcoma of the flat bones received combination chemotherapy. For the patient with tumor of the scapula, there was no evidence of tumor response before chemotherapy was discontinued. For another patient with osteosarcoma of the mandible, partial tumor resection

was performed prior to delivery; chemotherapy was given within 1 week of delivery, but was followed in 4 months by local recurrence of tumor. The young patient with osteosarcoma of the roof of the orbit had incomplete tumor resection followed by combination chemotherapy; he developed intractable heart failure and died after receiving five doses of adriamycin (cumulative dose, 280 mg/m^2).

A patient with large parosteal osteosarcoma of the femur has tolerated combination chemotherapy without unusual complications and remains free of metastases.

A patient with multifocal osteosarcoma which followed bilateral retinoblastoma (15) has tolerated chemotherapy without unusual complications, but has had progression of bony lesions which was followed by the development of bilateral pulmonary metastases 6 months after diagnosis.

DISCUSSION

Considerable attention has been directed toward the adjuvant treatment of osteosarcoma patients. This interest has been stimulated by the determination of the responsiveness of measurable metastatic lesions following administration of high-dose methotrexate-citrovorum factor or adriamycin (1,2,5,6,16). The extension of this information to the adjuvant treatment of patients following amputation prior to the development of metastases was obvious, and has been rewarding in that an estimated 50% of the patients will have a disease-free survival of > 18 months. Also, none of the nine patients surviving free of disease for ≥ 23 months has yet had a relapse or died. It is now also possible that patients who develop late metastases may achieve disease-free status for an additional extended period following resection of pulmonary metastases (7,17).

While there has been an importance placed on the dose requirements of both methotrexate (3) and adriamycin (4), it must be emphasized that the adjuvant chemotherapy for our group of 24 patients stressed combination chemotherapy using more moderate doses of methotrexate and adriamycin (with cyclophosphamide) extended over a period of time to encompass the period of maximum risk of developing pulmonary metastases. These doses have been associated with disease-free survival results which compare with those reported by others who have utilized higher doses of these agents (3–5). In comparison with other multiple-drug programs, similar toxic effects have also developed in our patients.

The two youngest patients in this group of 40 died following the development of drug toxicity, one associated with methotrexate and the other associated with adriamycin (11). Although age probably has little effect on the development of methotrexate toxicity, the patient who developed this drug toxicity had Down's syndrome and was shown to have delayed excretion of methotrexate (14). For the 4-year-old child who developed adriamycin cardiomyopathy, one must question the contribution of cyclophosphamide in the development of cardiomyopathy (18,19) since this patient had received only a 280-mg/m^2 cumulative dose of adriamycin. This dose is less than that reported by Prout et al (20) and by Lenaz and Page (21) in reviews of adriamycin cardiotoxicity in children and adults. Additionally, more than half of the patients in these reviews had received mediastinal or lung irradiation, and it may be assumed that the five patients with Ewing's sarcoma had received cyclophosphamide as prior or concurrent treatment.

Between 1973 and 1977, two fifths of the osteosarcoma patients admitted to our institution have been ineligible to receive "adjuvant" chemotherapy. These patients have had pulmonary metastases (either at or following diagnosis), nodal metastases, tumor of flat bones, osteosarcoma following radiotherapy, multifocal osteosarcoma, or parosteal osteosarcoma. Additional features which complicated or delayed the treatment of five patients were pregnancy in three patients and the extremely young age of two patients, one of whom had Down's syndrome. Each of these latter patients, who were not truly eligible to receive adjuvant chemotherapy, required individualized chemotherapy planning for his or her unique problem.

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High-Dose Methotrexate in Osteogenic Sarcoma: A 5-Year Experience[1]

Norman Jaffe,* Emil Frei III, Hugh Watts, and Demetrius Traggis[2]

SUMMARY

During the past 5 years, the combination of vincristine and high-dose methotrexate with citrovorum factor rescue (V-MTX-CF) was administered as adjuvant therapy to 20 patients with osteogenic sarcoma after local control of the primary lesion by amputation. The duration of treatment was 18–24 months. Twelve patients had "classic" osteogenic sarcoma; these patients have been followed from 39+ to 58+ months and seven have developed pulmonary metastases. A second group of 22 patients with classic osteogenic sarcoma received adjuvant treatment with V-MTX-CF and adriamycin (V-MTX-CF-ADR) administered 7 days after each V-MTX-CF course. This group has been followed from 18+ to 36+ months and six have developed pulmonary metastases. By life-table evaluation, 32% of the V-MTX-CF group and 64% of the V-MTX-CF-ADR group failed to develop pulmonary metastases. When compared to a historical control group of 78 previously treated patients in whom 82% developed pulmonary metastases, the difference in the incidence of this complication between the study and control curves is highly significant ($P < 0.001$). V-MTX-CF courses were also administered to patients with pulmonary or other metastases as a component of multidisciplinary treatment rendering 13 of 26 patients free of disease for 9+–54+ months. These data suggest that V-MTX-CF has had a major impact upon the biologic behavior of osteogenic sarcoma and if the trend continues, a significant difference in the cure rate can be anticipated.

[Cancer Treat Rep 62:259–264, 1978]

What progress has been forged in the treatment of osteogenic sarcoma with high-dose methotrexate (MTX)? This therapeutic regimen initially produced a response in five of 14 patients (35%) with metastatic disease (updated from original reports) (1,2). This regimen, alone and in combination with adriamycin (ADR), was then investigated as adjuvant treatment for eradication of microscopic disease (3,4). More recently, a weekly intensive program was utilized for the treatment of established metastases and preparatory to local en bloc resection for limb preservation (5,6). The programs are complex and potentially difficult; periodic examination to justify their continued administration is appropriate (7–9). This review will summarize the experience of the past 5 years and update results to June 1977.

High-Dose MTX Programs (Fig 1)

The high-dose MTX program originally devised by Djerassi has undergone minor modification. Vincristine (V) is administered ½ hour prior to the initiation of the 6-hour MTX infusion based upon reports that it promotes the uptake of MTX by tumor cells (10,11). After a 2-hour delay, citrovorum factor (CF) is initiated; 15 mg is administered iv at 3-hour intervals for 24 hours followed by 15 mg every 6 hours by the oral route. The first oral dose commences 3 hours after the last iv dose. The MTX doses are escalated from 3 to 7.5 g/m² at 2–3-week intervals and the 7.5-g/m² dose is then administered every 3 weeks for 18–24 months.

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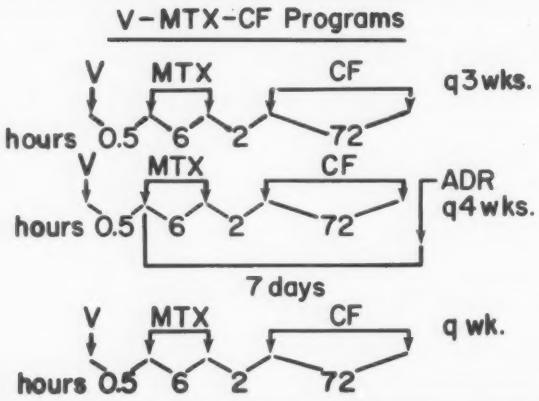

FIGURE 1.—V-MTX-CF programs. Doses are as follows: V, 2 mg/m² (maximum, 2 mg); MTX, 3, 6, and 7.5 g/m² (1st, 2nd, and subsequent doses, respectively); CF, 15 mg q3hrs iv for 24 hrs and q6hrs for 24 hrs; and ADR, 75 mg/m² (maximum cumulative dose, 450 mg/m²). (More recently, initial doses of MTX have started at 7.5 g/m².)

This regimen was administered as adjuvant treatment after primary definitive surgical therapy to 12 patients with classic osteogenic sarcoma with local control and to eight with other types, including four with the parosteal variety (3) (table 1). The study was terminated in June 197-.

V-MTX-CF-ADR

ADR was incorporated into the V-MTX-CF regimen after the latter was shown to be predominantly nonmyelosuppressive. It was administered 7 days after each V-MTX-CF course with the intervals between courses extended to 4 weeks. ADR was discontinued after a cumulative dose of 450 mg/m² and the every-3-week V-MTX-CF regimen was then reinstated. Adjuvant treatment was administered for 18 months.

This regimen was administered to 22 patients with classic osteogenic sarcoma following local surgical control (table 1). The study was activated in June 1974.

Weekly V-MTX-CF

The weekly regimen was developed after it was shown that V-MTX-CF could be delivered safely in a setting of intensive pharmacologic and toxicologic monitoring. The initial dose (recently standardized for all V-MTX-CF programs) commences at 7.5 g/m². Generally, four to eight weekly treatments are administered. The regimen is employed in the following categories:

1. Macrometastatic disease (5)
   a. preoperatively
   b. postoperatively
   c. postoperatively with radiation therapy for incompletely resected tumor
2. With radiation therapy for inoperable tumors (9)
3. Preoperatively in preparation for local en bloc resection of tumor (6)

Treatment-Related Studies and Procedures

Patients are hospitalized for each V-MTX-CF course. Pretreatment evaluation comprises a cbc count, liver function studies, creatinine clearance, and estimation of serum calcium, phosphorus, and magnesium. A cbc count, urinalysis, serum MTX, and creatinine are obtained daily during treatment and liver function studies at the completion of each course. Treatment is withheld in the presence of an

TABLE 1.—Characteristics of patients treated with adjuvant V-MTX-CF-ADR programs

Tumor type	No. of patients	Age (yrs) Range	Age (yrs) Median	Sex (M/F)	No. of patients with pulmonary metastases	Range of continuous disease-free period* (mos)	Median followup (mos)
V-MTX-CF study							
Classic†	12	8–20	13	7/5	7	42–58	46
Classic‡	3	10–15	15	1/2	2	58	
Parosteal	4	13–18	14	3/1	0	39–51	42
Multifocal	1	12		1/0	1		
Total	20						
V-MTX-CF-ADR study							
Classic†	22	6½–28½	12	12/10	6	18–36	23

* Includes only survivors who failed to develop pulmonary metastases.
† Local control achieved.
‡ Local control not achieved.

abnormal creatinine clearance, clinical jaundice, severe infection, mucositis, dehydration, and myelosuppression (leukocyte count < 2000/mm^3 and platelet count < 100,000/mm^3). Throughout the course, a continuous infusion of 5% dextrose in water in 0.2% saline is maintained to insure adequate hydration. Approximately 3 liters/m^2/24 hours are administered.

Liver function studies and hemograms are also obtained prior to each ADR treatment. An electrocardiogram, echocardiogram, and systolic ejection time are obtained prior to treatment and at regular intervals thereafter. The drug is withheld if there is any evidence of cardiac abnormality or in the presence of severe myelosuppression and grossly abnormal liver function studies.

General supportive measures comprise platelet transfusions for platelet counts < 25,000/mm^3, the empirical use of antibiotics for temperatures > 102° F in the presence of leukopenia, and wbc transfusions if infection is documented and if the polymorphonuclear leukocyte count is < 500/mm^3. Prophylactic mouth washes with Cepacol and hydrogen peroxide are utilized continually during V-MTX-CF treatments.

RESULTS

In the original study, one of the patients obtained a complete response (1,2) and remains alive, well, and free of disease 6 years later. Her normal, healthy baby, born 2½ years after discontinuation of treatment, shows no evidence of congenital abnormalities.

In the V-MTX-CF adjuvant study, five of the 12 patients with classic osteogenic sarcoma failed to develop pulmonary metastases (updated from original report) (3) (fig 2). In addition, five of the remaining eight patients, including four with the parosteal variety, remain free of disease. The survival period of the patients who did not develop metastases varies from 39+ to 58+ months (table 1 and fig 3). When compared to a historical control curve of 78 patients previously treated at the Sidney Farber Cancer Institute, the difference in the incidence of pulmonary metastases in the patients with classic osteogenic sarcoma and in the total group is highly significant ($P < 0.001$, by chi-square analysis). Eighty percent of the control group developed pulmonary metastases within 12 months.

Pulmonary metastases which developed in four of the patients with classic osteogenic sarcoma were removed surgically and all patients currently remain free of disease. Two patients in this group were included in a previous report (5). One of these patients developed an osteogenic sarcoma in the contralateral nonamputated femur 1 month following cessation of treatment at 18 months. This was resected and replaced by an internal prosthesis. One additional patient is alive with widespread disease; following a severe anaphylactic reaction to MTX 1 year after diagnosis, additional therapy was refused. The survival in patients who did not develop pulmonary metastases varies from 42+ to 58+ months (table 1 and fig 3).

Adjuvant V-MTX-CF-ADR

Six of the 22 patients developed metastases (fig 2). The results are similar to the V-MTX-CF adjuvant trial ($P < 0.001$). Three patients have died, one was rendered free of disease by multidisciplinary treatment (5), and the other two are being treated for pulmonary and bone metastases with the addition of *cis*-dichlorodiammineplatinum(II) to V-MTX-CF. The survival period of the patients who did not develop metastases varies from 18+ to 36+ months (table 1 and fig 3). Treatment has been discontinued in all patients.

Weekly V-MTX-CF

Macrometastatic Disease

The tactics and strategy of management for patients in this category have been published (5). Essentially, attempts are made to achieve a no evidence of disease (NED) status with weekly V-MTX-CF. Metastases which fail to respond are removed surgically. After NED has been achieved, the every-3-week V-MTX-CF schedule is administered on the assumption that this could still be effective against residual microscopic disease. Patients who have not received ADR are also treated with this chemotherapeutic agent. The total duration of treatment is 18–24 months.

In the initial studies, 15 of 21 patients were rendered free of disease and 14 had NED for 2+–18+ months (5). To date, ten of the 14 patients remain free of disease for periods varying from 9+ to 54+ months. Pulmonary metastases which recurred in two patients were again removed surgically and treatment was replaced by *cis*-dichlorodiammineplatinum(II). Also, since publication of the original report, five additional patients with pulmonary metastases have been treated; one died, a second is alive with disease, and three have been rendered free of metastases with the multidisciplinary approach.

One patient with an inoperable tumor of the pelvis was treated with radiation therapy (4000

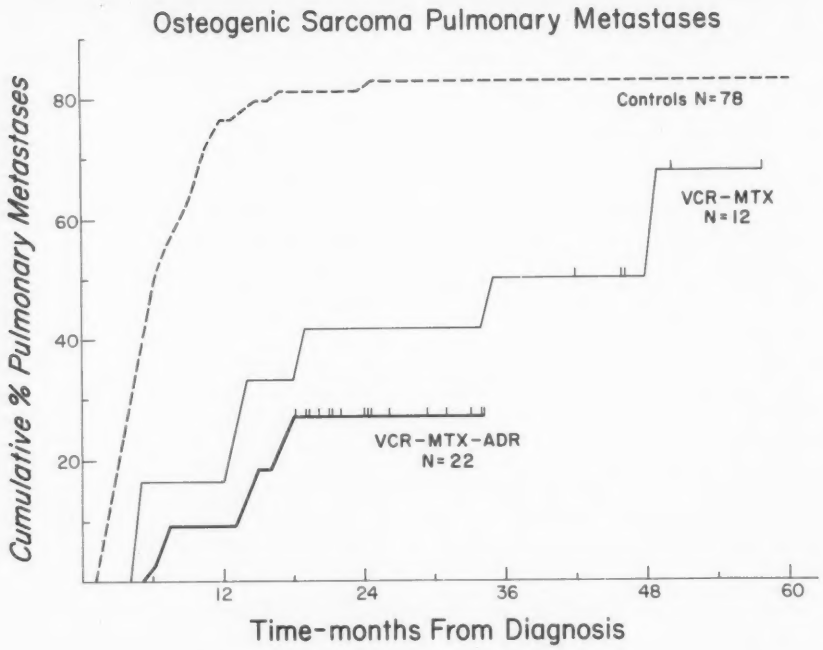

FIGURE 2.—Adjuvant chemotherapy for osteogenic sarcoma. All patients had classic osteogenic sarcoma with local control achieved by amputation.

rads/Fx 20/28 days) and weekly V-MTX-CF (9). A partial response was obtained and the tumor eventually calcified. He had previously received < 3000 rads to the tumor concurrently with ADR at another institution. Treatment was discontinued after 14 months. Pulmonary metastases were detected 20 months later although local control was apparently still present. He remains alive with pulmonary metastases 26 months after discontinuation of treatment.

Survival (Fig 3)

The effect of adjuvant chemotherapy is ultimately reflected in survival. By life-table analysis, 38% of patients are continuously disease-free and 70% are disease-free after the application of multidisciplinary treatment. The overall survival rate is 82% ($P < 0.001$).

Toxicity

There has been no major change in the incidence and character of toxicity, as reported earlier (12). However, an acute anaphylactic reaction to MTX occurred in two patients. This manifested as urticaria and tingling sensations in the palms and soles. It recurred several times despite pretreatment with Solu-Cortef and antihistamines. MTX desensitization was then successfully accomplished in both patients and treatment was reinstated; this was well tolerated in one patient but anaphylaxis and hypotension recurred in the second and further therapy was refused.

Management of Primary Tumor (Ref 13)

Transmedullary amputation was performed for lesions located in the middle and distal parts of the long bones. The level of amputation was set at 7 cm above the uppermost reactive site visualized on bone scanning of the affected limb. Among 28 patients so treated, none developed local recurrence. There was no difference in the incidence of pulmonary metastases in patients treated by transmedullary amputation or disarticulation or forequarter amputation.

Limb preservation in selected patients is reported in a companion paper in this issue.

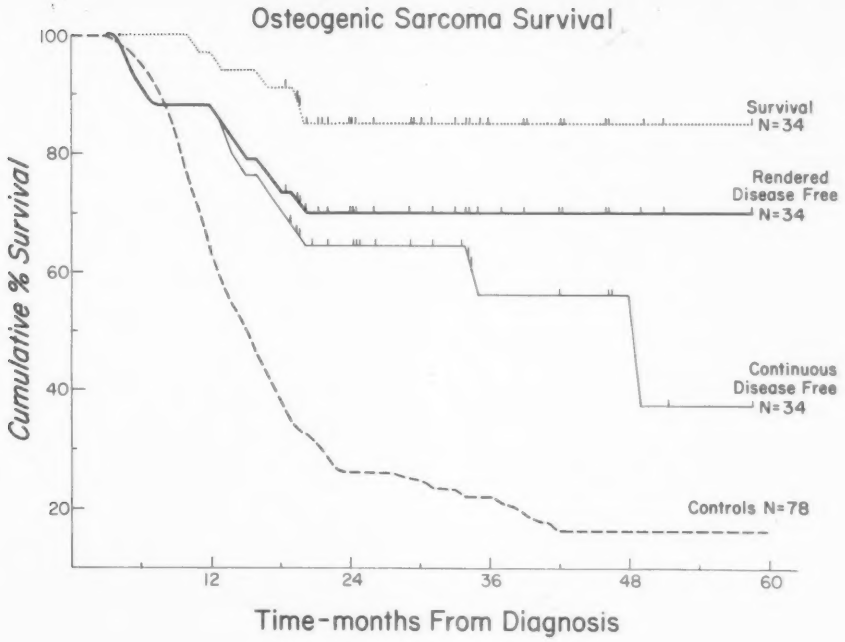

FIGURE 3.—Survival in patients with classic osteogenic sarcoma with local control achieved by amputation. A. Total survival. B. Survival of patients who are currently disease-free. Includes patients who are continuously disease-free and those who developed metastases but were subsequently rendered disease-free by multidisciplinary treatment. C. Patients continuously disease-free who failed to develop pulmonary metastases.

DISCUSSION

Major progress appears to have been achieved in the treatment of osteogenic sarcoma with the V-MTX-CF programs. Application of the latter has improved survival by reducing the incidence of pulmonary metastases and eradicating established disease and has provided innovative approaches to the management of the primary tumor. The differences in the incidence of pulmonary metastases must be interpreted in the framework of the perennial controversy surrounding historical controls. Thus, most investigators record that a 20% survival for osteogenic sarcoma may be expected in optimum circumstances (14–16). However, one institution has claimed that such survival may be as high as 40%–50%.[3] Further periods of observation and analysis may be warranted.

Considerable controversy surrounds the use of transmedullary amputation as opposed to disarticulation in the management of the primary tumor of the long bones. The latter has been recommended in an effort to avert stump recurrences due to "skip" lesions (17). However, this complication was not encountered in any of the patients treated by transmedullary amputation and adjuvant chemotherapy. This may have been due to an absence of skip lesions (as determined by radionucleotide scanning) and/or the efficacy of the adjuvant programs.

Multidisciplinary intervention was employed with increasing frequency, particularly since effective adjuvant treatment appeared to have changed the pattern and character of pulmonary metastases in patients who relapsed; these appeared to be limited in number and delayed in appearance (an observation also noted by others) (18). Additional patients were consequently rendered free of disease (fig 3). Overall, the results of the 5-year experience are

[3]Mayo Clinic, Rochester, Minn. Unpublished data.

encouraging and if the trend continues, a substantial escalation in the cure expectancy for patients with osteogenic sarcoma may be anticipated.

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Multidrug Adjuvant Chemotherapy for Osteosarcoma: Interim Report of the Southwest Oncology Group Studies [1]

Wataru W. Sutow,[2,*] Edmund A. Gehan,[2] Paul G. Dyment,[3] Teresa Vietti,[2] and Thomas Miale [4]

A four-drug adjuvant chemotherapy program (cyclophosphamide, vincristine, melphalan, and adriamycin), designated as the CONPADRI-I regimen, was initiated in patients with nonmetastatic osteosarcoma by investigators of the Southwest Oncology Group (SWOG) in June 1970. The regimen was modified to COMPADRI-II by the addition of three pulses of high-dose methotrexate in May 1973. Subsequently, the regimen was again amended to COMPADRI-III in February 1976 by intensifying the adriamycin dose. The present interim report updates, through September 15, 1977, the data previously published (1,2).

TREATMENT REGIMENS

Each patient had a histologically verified diagnosis of osteosarcoma; none had any evidence of metastases at the start of chemotherapy. All patients had had surgical amputation for the primary lesion.

Schematic representations of the three chemotherapy regimens are shown in figures 1, 2, and 3. The drug dosages among the three regimens are compared in table 1.

RESULTS

The numbers of patients entered into the study for the various regimens have been summarized in table 2. For COMPADRI-III, only patients registered prior to September 1, 1976, have been tabulated.

Figure 4 gives the disease-free survival experience for patients receiving CONPADRI-I, COMPADRI-II, and COMPADRI-III. Patients who were not eligible or not evaluable have not been included in the curves. However, patients treated with COMPADRI-II who were partially evaluable have been included; the three patients reported as having toxic deaths were considered to be relapses from disease-free survival on the date of death. Other partially evaluable patients were considered to be disease-free until they were removed from the study.

Table 3 gives the percentages of patients disease-free at 1 and 2 years after the start of the study. The percentages at 1 year were 59% for CONPADRI-I, 63% for COMPADRI-II, and 66% for COMPADRI-III. A generalized Wilcoxon test (3) of the differences between disease-free survival curves among the three drug regimens yielded the following: I vs II, $P = 0.74$; II vs III, $P = 0.37$; I vs III, $P = 0.68$. Hence, there is no real evidence from this test that the disease-free curves differed among groups. Note that the median followup time differs substantially between studies (table 3).

The disease-free survival curves on semilog paper plot nearly as a straight line, except for patients in the CONPADRI-I study where no patients relapsed after 16 months. Survival curves plotting as a straight line on semilog paper indicate that the data are exponentially distributed. If one assumes that the data are exponentially distributed, the relapse rates per month are given with their standard errors (SE) in table 3. Note that the relapse rates are substantially higher with COMPADRI-II and COMPADRI-III, primarily reflecting the fact that there have been no relapses after 16 months with CONPADRI-I. If one carries out an F test of the differences between curves using the assumption of the exponential distribution, the significance levels for the possible tests for the three study regimens are as follows: I vs II, $P < 0.05$; I vs III, $P < 0.01$; II vs III, $P \simeq 0.20$. Hence, using the exponential distribution assumption means that there may be some real differences between I vs II and I vs III. As mentioned above, the main difference between curves arises after 16 months and this is where there is the most evidence that the exponential distribution may not be correct. Hence, the test based on the exponential distribution would have to be regarded as preliminary. Further followup would be needed on study groups II and III to determine whether there will be relapses after 30 months.

[1] Supported in part by Public Health Service grants CA-03713, CA-04919, CA-05587, CA-16943, CA-12014, and CA-02501 from the National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare.

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TABLE 1.—Comparison of therapy regimens

Drug	CONPADRI-I (SWOG-979)*	COMPADRI-II (SWOG-7317)	COMPADRI-III (SWOG-7317/2)
Vincristine (No. of doses)	12	15	14
Cyclophosphamide	10 mg/kg/day × 7 for 3 courses	Same	Same
Adriamycin (cumulative dose)	390 mg/m²	120 mg/m²	360 mg/m²
Melphalan	0.3 mg/kg × 4 pulses	Same	× 3 pulses
Methotrexate	None	3 pulses (75, 100, and 150 mg/kg)	3 pulses (75, 150, and 200 mg/kg)

*SWOG study designation.

TABLE 2.—No. of patients studied

	CONPADRI-I	COMPADRI-II	COMPADRI-III
Study opened (date)	6/20/70	5/14/73	2/27/76
Study closed (date)	10/15/74	1/28/76	Current
No. of patients—			
Registered	56	67	51
Not eligible/not evaluable			
Metastatic at diagnosis	8	5	2
Not osteosarcoma	1		1
Treatment not given	3	1	2
Treatment late		1	
Not amputated			2
	12	7	7
Eligible/evaluable	44	60	44

TABLE 3.—Results of 3 regimens

Treatment	No. of evaluable patients	No. of patients relapsing	% of patients disease-free at—		Median followup time (mos)	Relapse rate/mo	SE
			1 yr	2 yrs			
CONPADRI-I	44	20	59	55	37	0.0134	0.0030
COMPADRI-II	60	33*	63	51	21.5	0.0266	0.0046
COMPADRI-III	44	22	66	42	14.5	0.0364	0.0078

*Includes 3 patients classified as toxic deaths.

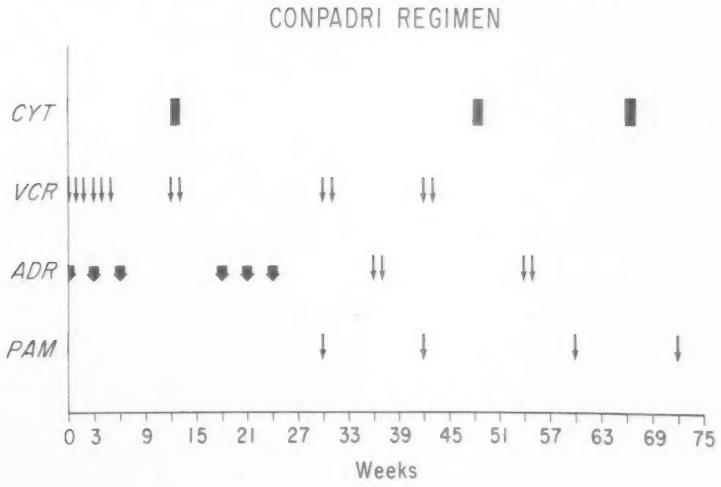
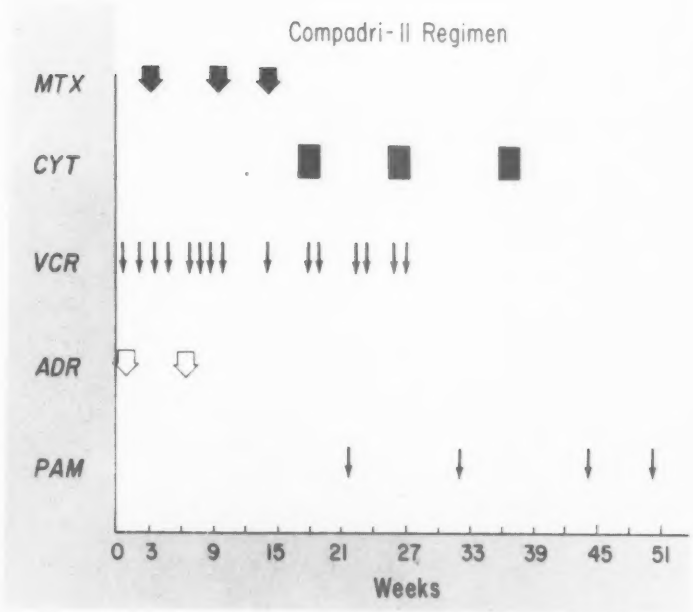


FIGURE 1.—Schema for CONPADRI-I.



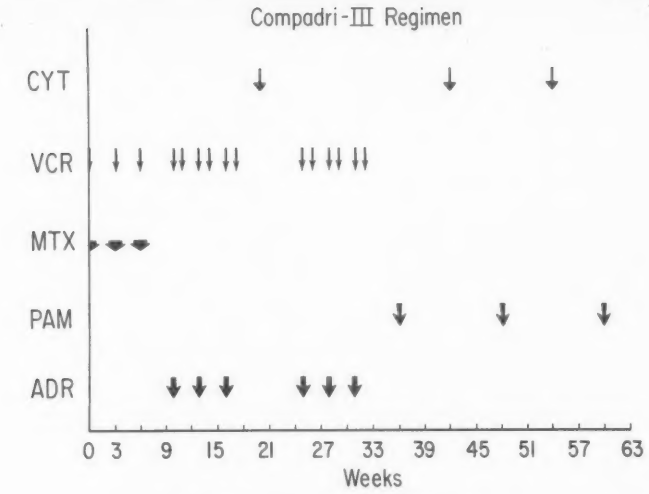


FIGURE 3.—Schema for COMPADRI-III.

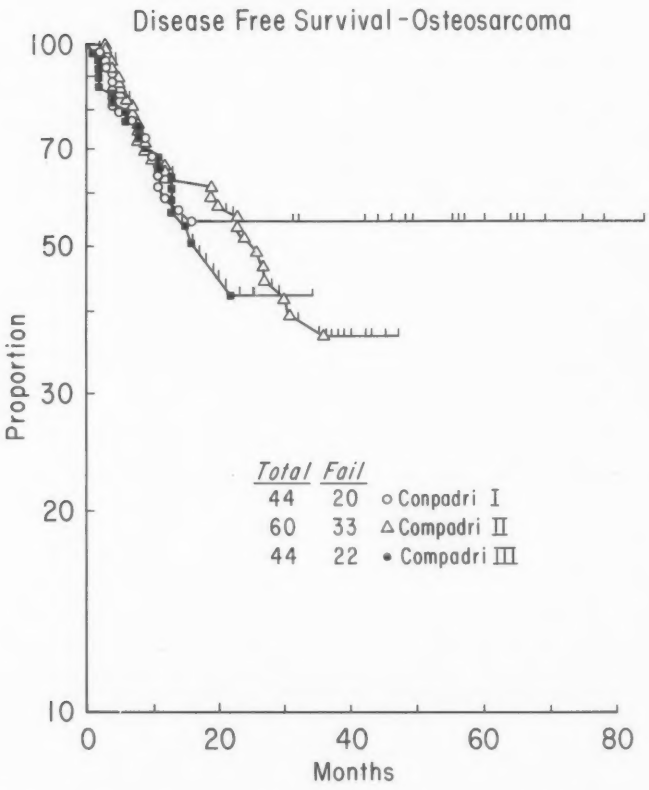


FIGURE 4.—Disease-free survival for patients receiving adjuvant chemotherapy with CONPADRI-I, COMPADRI-II, and COMPADRI-III regimens.

DISCUSSION

When methotrexate was first utilized in these studies (COMPADRI-II), the drug was administered as a continuous iv drip over a period of 24 hours. Severe toxic effects occurred in some patients and three patients died from drug-related problems. Subsequently, the period of administration was shortened to 6 hours. Careful attention was paid to fluid intake, and the urine was alkalinized. Methods to monitor blood levels of methotrexate were introduced. There have been no further deaths from toxicity, which has been well within acceptable limits.

The problem of late metastases (after 18 months) became strikingly noticeable in the COMPADRI-II study (4). Of the 30 patients who developed metastases, 12 relapsed after 18 months. The actual disease-free intervals until metastases in these 12 late failures were: two patients at 19 months, one at 20 months, two at 23 months, one at 24 months, one at 26 months, two at 27 months, and one each at 30, 31, and 36 months.

These data would suggest that (*a*) the period of risk for development of late metastases must be reevaluated for patients with osteosarcoma surviving without metastases, (*b*) the chemotherapy effect on survival curves may reflect, in part, altered biologic behavior of the tumor as the result of therapy (5), and (*c*) most patients must be considered still in a risk category if the followup period is < 36 months.

As data from the COMPADRI-III study became available, the adjuvant chemotherapy regimen was intensified (COMPADRI-IV) by: (*a*) increasing the methotrexate dose to 250 mg/kg, (*b*) increasing the frequency of the methotrexate schedule to two weekly doses for each of the first three courses, and (*c*) adding three courses of methotrexate and two doses of adriamycin during the last half of the chemotherapy program.

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Amputation and Adriamycin in Primary Osteosarcoma: A 5-Year Report [1,2]

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Adriamycin, a cytotoxic antibiotic derived from *Streptomyces peucetius* var. *caesius*, was introduced in the US for clinical trials by Farmitalia (Milan, Italy) in 1968. In 1972, we initially reported the activity of adriamycin in a small series of patients with osteosarcoma that had metastasized to the lungs (1,2). Encouraged by this therapeutic result in metastatic osteosarcoma, the CALGB reported the preliminary results of a study initiated in 1971 using intermittent adriamycin treatment shortly after radical surgical amputation of primary osteosarcoma in an effort to apply chemotherapy when the body burden of tumor cells was lowest (3,4).

The present paper reports the 5-year followup of amputation and adriamycin in primary osteogenic sarcoma undertaken by the CALGB.

METHODS AND MATERIALS

The criteria for entry in the study included: (*a*) histologically proven osteosarcoma, characterized by osteoid or bone apposed to tumor cells (none of the patients had parosteal osteosarcoma, chondrosarcoma, fibrosarcoma, radiation-induced osteosarcoma, or osteosarcoma after Paget's disease, all of which have different clinical courses) (5); (*b*) surgically resectable primary tumor without roentgenologic evidence of metastases; (*c*) a minimum leukocyte count of 4000/mm^3 and platelet count of 100,000/mm^3; and (*d*) BUN and creatinine levels < 25 and 1.5 mg/100 ml, respectively.

Hematologic, biochemical, and electrocardiographic examinations, chest roentgenogram and tomography, and bone survey were conducted before, during, and after therapy to monitor for possible tumor recurrence and drug toxicity.

Drug Dosage and Schedule

Adriamycin is supplied in 10-mg vials. Each vial was diluted with 5 ml of sterile saline and the calculated dose was injected as an iv bolus.

Four to 14 days after amputation of the primary lesion, or as soon as wound healing was complete, adriamycin was given at a dose schedule of 30 mg/m^2/day for 3 successive days repeated every 4–6 weeks for six courses. The total cumulative dose of adriamycin was 540 mg/m^2 over a period of 5–7 months. Thereafter, patients remained untreated.

The response to therapy was measured by the disease-free interval after the first course of adriamycin. Treatment failure was defined as unequivocal roentgenologic evidence of disease recurrence.

A leukocyte count of < 1000/mm^3 resulting from adriamycin administration required the reduction of succeeding doses of adriamycin to 25 mg/m^2/day for 3 days. No dose adjustment was to be made if the leukocyte count nadir was > 1000/mm^3 unless an accompanying complication such as septicemia occurred. Any reduction of adriamycin dose at this leukocyte count nadir was considered a dose violation.

Radical amputation, ie, complete removal of the involved bone, was required. Cross-bone amputation of the involved long bone is an inadequate procedure and was considered a surgery violation.

From November 1971 to December 1975, 102 patients from 21 institutions were entered in the study. Fourteen patients were disqualified; six had overt metastases, four never received adriamycin, and one each had parosteal osteosarcoma, osteosarcoma arising from Paget's disease, inadequate records, and sequential adriamycin and high-dose methotrexate treatment. The remaining 88 patients form the basis of this report.

RESULTS

Of the 88 patients there were 52 males and 36 females. Their ages ranged from 4 to 66 years, with a mean and median age of 14 and 15 years, respectively.

The primary sites of osteosarcoma in these 88 patients are shown in table 1. The lesion in 65 patients (73%) was localized around the knee joint.

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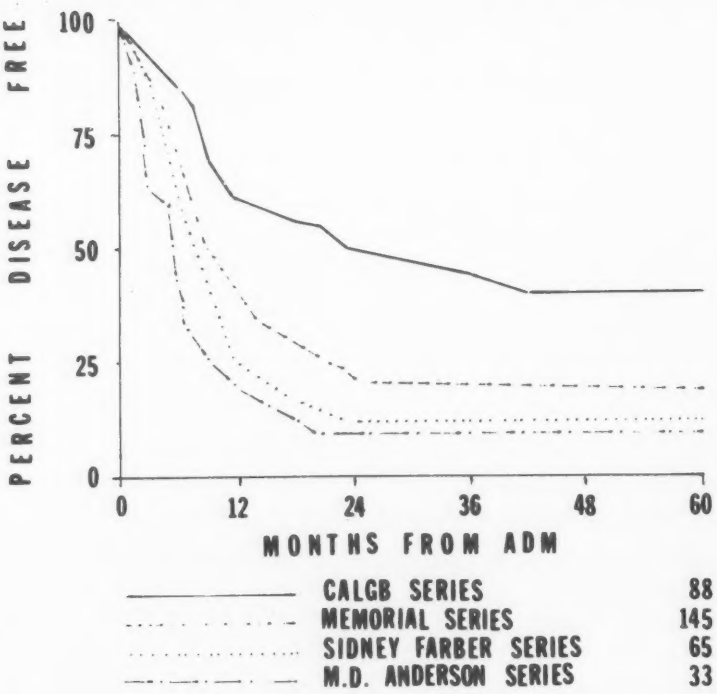

FIGURE 1.—% of patients with osteosarcoma remaining disease-free after surgery alone (3 historical controls) and surgery followed with adriamycin (CALGB series).

The CALGB has no historical control of its own in primary osteosarcoma treated with surgery alone. We use the data reported by Marcove et al (6), Jaffe et al (7), and Sutow et al (8) as historical comparison groups. In these three series, approximately 20% of the patients were free of metastases at 60 months. The median onset of pulmonary metastases occurred at 6–8.5 months (fig 1).

In the adriamycin-treated group, 43 of 88 patients (48.8%) had relapsed (38 pulmonary metastases, three local recurrences, and two bone metastases). At 60 months, 39% of the treated patients were expected to be free of disease as determined by the life-table method. The median onset of recurrence was 20 months (fig 1).

Table 2 shows the characteristics of 88 patients with or without protocol violations. There were slightly more patients < 16 years old and with lesions arising from the femur in the protocol violation group. In contrast, lesions arising from the tibia and fibula were more frequent in the no violation group. The remaining listed characteristics seemed to be comparable between the two groups, including mean days from diagnosis to surgery, mean days from surgery to adriamycin, and percentage of various tumor sizes.

For reasons unrelated to a nadir of leukocytes < 1000/mm^3, 16 of the 88 patients had their adriamycin dose reduced. Ten of these 16 (62.5%) have relapsed. Of 17 patients whose involved bones were not completely removed and of eight who had both inappropriate dose reduction of adriamycin and a subradical surgical procedure, 11 (64.7%) and six (75%) have relapsed, respectively. No protocol violation in terms of dose or extent of amputation occurred in 47 patients in the present series; among these 47 patients, 16 (34%) have relapsed. The following characteristics influenced disease-free status as projected by the life-table method at 4 years: (*a*) adriamycin dose violation, 22%; (*b*) surgery violation, 28%; (*c*) adriamycin dose and surgery violation, 18%; and (*d*) no violation (full adriamycin dose and complete removal of involved bone), 51% (fig 2).

The probability that the total groups with protocol adherence and protocol violation would have this disparate relapse rate on chance alone is remote ($P < 0.003$).

Pulmonary metastases appeared in 17 of 88 pa-

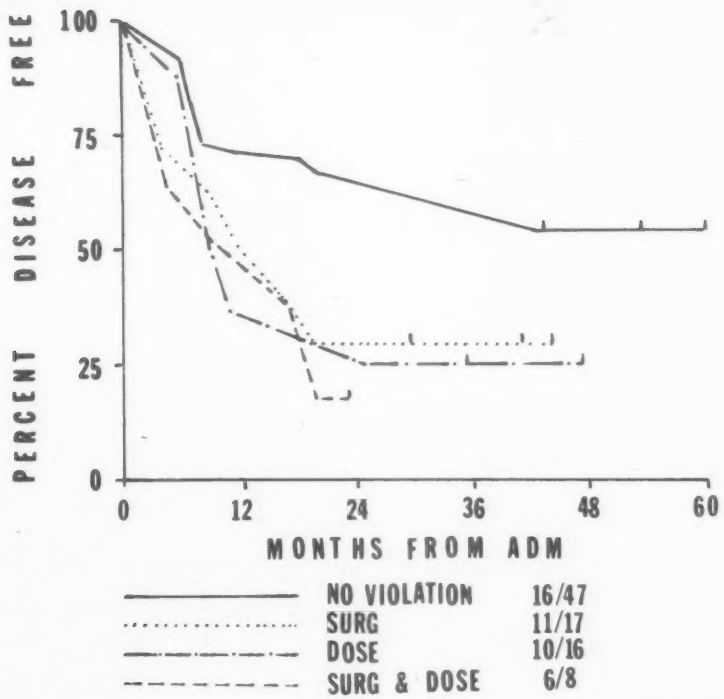

FIGURE 2.—% of patients with osteosarcoma remaining disease-free after surgery and adriamycin according to protocol violation (vertical lines = individual patients free of disease from the last relapsing patient).

TABLE 1.—Frequency of primary site

Site	No. of patients
Femur	
Distal	44
Middle	3
Tibia	
Proximal	21
Distal	5
Fibula, proximal	4
Humerus	6
Rib	3
Mandible	1
Iliac spine	1
Total	88

TABLE 2.—Characteristics of 88 osteosarcoma patients according to protocol violation

Category	No protocol violation	Protocol violation
Total No. of patients	47	41
Mean days from diagnosis to surgery	12	10
Mean days from surgery to adriamycin	23 (20% > 21)	21 (15% > 21)
Mean age in yrs	18 (42% < 16)	21 (66% < 16)
Males (%)	62	56
	No. of patients (%)	
Tumor site		
Femur	18 (38)	29 (70)
Tibia	18 (38)	8 (20)
Fibula	4 (9)	0 (0)
Humerus	4 (9)	2 (5)
Other	3 (3)	2 (5)
Tumor size (cm)		
< 5	10 (28)	6 (24)
5–10	16 (46)	11 (44)
> 10	9 (26)	8 (32)
Size not recorded	12	16

tients before the completion of six courses of adriamycin therapy. Of 46 patients who have been observed for ≥ 1 year, nine (19.5%) have relapsed. After ≥ 2 years, only one of 22 patients (4.5%) has developed pulmonary metastases, and this occurred at 42 months after the start of adriamycin therapy.

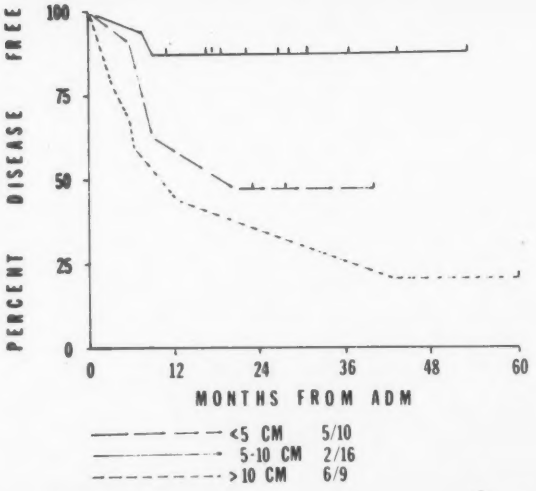

FIGURE 4.—% of patients with osteosarcoma remaining disease-free after surgery and adriamycin (no protocol violation) according to primary tumor size (vertical lines = individual patients free of disease from the last relapsing patient).

The higher recurrence rates of patients violating the protocol compared to those who were properly treated held true regardless of primary site, sex, and age. While such factors as femur versus tibia-fibula and male versus female did not show significant difference in disease-free interval, the group of patients < 16 years old treated according to the protocol had a longer projected disease-free interval

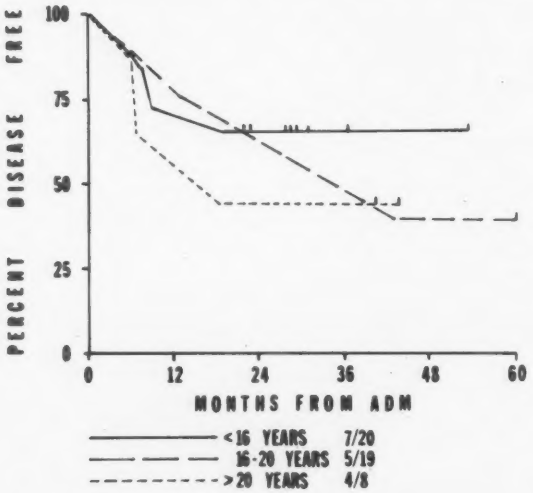

FIGURE 3.—% of patients with osteosarcoma remaining disease-free after surgery and adriamycin (no protocol violation) according to age (vertical lines = individual patients free of disease from the last relapsing patient).

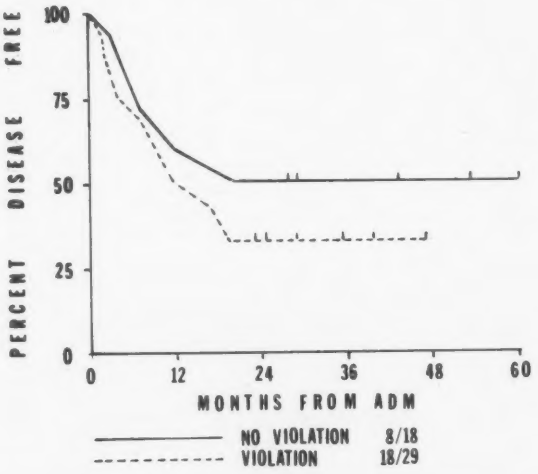

FIGURE 5.—% of patients remaining disease-free with osteosarcoma arising from femur with or without surgery and/or adriamycin dose violation (vertical lines = individual patients free of disease from the last relapsing patient).

TABLE 3.—Characteristics of 47 osteosarcomas arising from the femur according to protocol violation

Category	No. of patients (%)	
	No protocol violation	Protocol violation
Total	18	29
Sex		
Males	12(66)	18(62)
Females	6(33)	11(38)
Age (yrs)		
< 16	9(50)	19(65.5)
16–20	6(33)	8(27.5)
> 20	3(16.6)	2(6.8)
Mean	20 yrs	14 yrs
Median	15 yrs	14 yrs
Tumor size (cm)		
< 5	2(14)	5(26)
5–10	7(50)	9(47)
> 10	5(30)	5(26)
Size not recorded	4	10

than patients > 16 years old. At 48 months, 62.5% of the patients < 16 years old were expected to be disease-free compared to 37% of those > 16 years old (fig 3). The better prognosis of patients < 16 years old compared to older patients was also seen in the protocol violation group.

The disease-free interval for patients with primary tumors of various sizes treated according to the protocol is shown in figure 4. At 48 months, 87% of the lesions ranging from 5 to 10 cm in maximum diameter were expected to be free of disease. In contrast, tumor lesions < 5 or > 10 cm in diameter had projected disease-free status in substantially fewer patients.

The characteristics of the primary tumors arising from the femur in 47 patients with or without protocol violation are shown in table 3. A greater number of cases and a higher percentage of patients < 16 years old with tumor lesions < 5 cm in diameter were found in the protocol violation group compared to the protocol adherence group. The remaining listed characteristics seemed to be comparable between the two groups including mean days from diagnosis to surgery, mean days from surgery to adriamycin, ratio of males to females, and percentage of tumor lesions ranging from 5 to 10 cm in diameter. At 48 months the disease-free interval in the protocol violation group was predicted to be 31%, but was 48% in the protocol adherence group (fig 5).

Pulmonary metastases are usually the first evidence of recurrent osteosarcoma. The published data of Marcove et al (6) on 145 patients < 21 years old with operable osteosarcoma of the extremities were used for the historical comparison group. Only 19% were free of pulmonary metastases at 60 months after surgery. In the present series of 39 patients < 21 years old treated with a full adriamycin dose and complete removal of the involved long bone, 52% were projected to be free of pulmonary metastases at the same period of time.

Toxicity

The toxicity from adriamycin was tolerable. Transient capital alopecia occurred in 100% of the patients, leukopenia (< 3000 cells/mm^3) occurred in 60%, nausea and vomiting occurred in 50%, and stomatitis occurred in 45%. Pneumonia occurred in one patient. In another patient, delayed wound healing complicated by a wound infection was noted during adriamycin administration. Transient electrocardiographic changes in the form of premature atrial and ventricular beats occurred in 10%. Twenty of the 88 patients did not finish six courses of adriamycin because of relapse (18 patients) or refusal (two patients). Of the 68 patients who finished the six courses of adriamycin, two developed congestive heart failure. One patient had a simultaneous onset of fatal pulmonary metastases and congestive heart failure 2 months after the completion of 540 mg/m^2 of adriamycin. At autopsy, a mural thrombus in the ventricle and interstitial fibrosis of the myocardium were noted. The other patient developed irreversible congestive heart failure 3 months after 540 mg/m^2 of adriamycin was completed. She died 1 month after the onset of heart failure. At autopsy, a metastatic lesion to the heart and metastases in the lungs were demonstrated which had not been previously noted by roentgenographic studies.

A girl who completed the six courses of adriamycin at 16 years of age delivered a normal child at age 21 years.

DISCUSSION

In osteogenic sarcoma, surgery alone or in combination with radiotherapy has repeatedly achieved a 5-year survival rate of approximately 20% (9). Although there is unanimous agreement that cross-bone amputation of the femur is the proper surgery for osteosarcoma arising from the proximal tibia, there are arguments regarding the level of amputation for lesions arising from the distal femur. Nevertheless, regardless of the type of surgical procedure, the 5-year survival rate of patients with lesions arising from the femur remains the same (10). Local recurrence in the femoral stump, however, occurred in seven of 38 patients (16%) treated

by amputation through the femur as reported by Sweetnam (11), whereas disarticulation of the hip for femoral tumor in 30 patients was accomplished without local recurrence. This finding supports the "skip" metastases reported by Enneking and Kagan (12). They demonstrated that simultaneous, secondary, smaller foci of osteosarcoma, anatomically separate from the primary lesion, occurred in ten of 40 osteosarcoma patients.

In our present series, no local recurrence occurred in 63 patients (47 with no violations and 16 with dose violations) whose involved long bones were completely removed. One patient, however, had contralateral tibial metastases at 9 months and another with dose violation had tumor extension to the homolateral acetabulum at 8 months from a primary osteosarcoma arising during pregnancy in the distal femur. Twenty-five patients had less than radical surgery. Of 23 patients in this group with osteosarcoma of the long bones, one local recurrence appeared at 19 months. Local recurrences also appeared in two patients with osteosarcomas involving the iliac spine and mandible. In both of these patients it is assumed that the relapses were due to limitations of the extent of radical surgery.

From our previous experience with metastatic disease, bone recurrences have been found to be quite resistant to treatment with adriamycin. In the present series, 11 relapses occurred (ten pulmonary and one local) in a group of 17 patients who had subradical surgery despite full doses of adriamycin. Therefore, it is possible that the remaining unresected involved bone contained "skip" lesions or micrometastases not completely eradicated by adriamycin, which were responsible for the pulmonary metastases and local recurrence upon termination of therapy. Whether this observation is also true in other adjuvant chemotherapeutic programs is not known.

Lowering the dose of adriamycin to avoid leukopenia was also associated with a higher recurrence of disease as compared with patients who received full adriamycin doses. This extremely dose-dependent antitumor activity of adriamycin is consistent with our earlier reports in metastatic osteosarcoma (1,2,4). Further evidence that this adriamycin dose-dependent antitumor activity exists in osteosarcoma was confirmed by Gottlieb.[6] He reported that all five patients with primary osteosarcoma treated by amputation and adriamycin at 50 mg/m²/course every 3 weeks developed pulmonary metastases.

The finding by Scranton et al (13) of a better prognosis in females than in males with osteosarcoma treated with surgery alone is not seen in our adriamycin-treated patients. McKenna et al (5) reported that tumor size correlated well with survival of the patients. In their series, osteosarcoma patients with lesions < 5 cm in diameter had a 40% 5-year survival rate compared to a 17%, 4%, and 0 survival rate in patients with lesions from 5 to 10, from 10 to 15, and > 15 cm, respectively. In our present report, it is uncertain why patients with a tumor of < 5 cm in diameter had a shorter disease-free interval than those with lesions ranging from 5 to 10 cm. As might be expected from McKenna's data, patients with lesions > 10 cm in diameter had the worst prognosis despite the full adriamycin dose and the complete removal of the involved bone, with only 19% of the patients expected to survive for 5 years.

The conclusion that full doses of adriamycin and complete removal of the involved bone in osteosarcoma are the most effective ways to assure successful adjuvant therapy is supported by a longer disease-free interval in patients without protocol violation compared to those with protocol violation in every prognostic category. This conclusion is reinforced by the effect of therapy in lesions of a single site, the femur. Despite less favorable balance of prognostic factors such as age and tumor size, the disease-free interval in the protocol adherence group is still significantly longer than in patients who violated the protocol. Two of 68 patients receiving 540 mg/m² of adriamycin developed congestive heart failure, however, both of these patients were found to have pulmonary metastases which may have contributed to their cardiac dysfunction.

Whether the delayed recurrence observed for up to 5 years in this report will result in cure remains to be proved in 1 or 2 years of further followup. The fact that only a single relapse has occurred so far after 2 years of observation lends credence to this proposition. The failure to adhere to the protocol and the appearance of metastases in 50% of the patients, despite meticulous application of the treatment, clearly indicate this is only a step along the way, and we are now investigating other programs.

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Adjuvant Treatment With Adriamycin in Primary Operable Osteosarcoma

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The cure rate achieved with local treatment modalities (amputation, radiotherapy, or both) in clinically localized osteogenic sarcoma does not usually exceed 20% (1). In fact, most patients show progressive clinical evidence of lung metastases during the first 12 months following surgery with median disease-free survivals ranging from 6 to 10 months (1–3). This high incidence of early clinical dissemination has prompted many investigators to administer as adjuvant treatment those chemotherapeutic agents which have been proven to be effective in inducing objective response in patients with radiologic evidence of distant metastases (1). The intent of the combined treatment approach is to eradicate the subclinical foci of disease which are present in most patients at the time of initial diagnosis (2–4).

Adriamycin (ADM) is known to be one of the most effective drugs in the treatment of advanced osteosarcoma (5,6). For this reason, since 1974 we have combined ADM with radical surgery as an adjuvant treatment for clinically localized osteosarcoma.

PATIENTS AND METHODS

From March 1974 to January 1977, 13 consecutive patients with histologically proven diagnosis of "classic" osteogenic sarcoma were treated in our institute with amputation followed by ADM. Two other patients with the histologic diagnosis of parosteal osteosarcoma were also treated with this approach. In ten of 13 patients the age ranged between 10 and 15 years.

After amputation, ADM was injected as a single iv dose of 75 mg/m^2. In the absence of treatment failure, chemotherapy was continued in the outpatient clinic every 4 weeks for a total of 6 to 8 months. The total dose of ADM was planned not to exceed 600 mg/m^2. At this time, all patients but one have completed their adjuvant chemotherapy. In those who have completed chemotherapy, a median of eight cycles of ADM were administered with a median total dose of 525 mg/m^2.

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RESULTS

Table 1 summarizes the most important clinical data related to treatment and survival. As of March 3, 1977, six patients have relapsed at 1, 4, 8, 18, 21, and 32 months following amputation. Seven patients remain continuously free of disease from 2+ to 36+ months. In contrast, three of six patients with relapse have already died of progressive disease after 5, 6, and 8 months, respectively, from the diagnosis of primary treatment failure. None of the four patients treated with transmedullary amputation showed local recurrence in the stump. One patient had lung metastases 1 month after surgery. New manifestations of disease were documented in the lungs in four patients and in the skeleton (humerus and sacrum) in two patients. Two patients relapsed while receiving chemotherapy. The other four patients relapsed once ADM was discontinued. Disease-free survival could not be correlated to duration of symptoms before surgery, site of initial involvement, type of surgery, or interval between amputation and start of chemotherapy.

Neither of the two patients with parosteal sarcoma showed recurrence 10+ and 33+ months after amputation.

Treatment with ADM was, in general, well tolerated and dose reductions were seldom required. No patient showed a leukocyte count $< 1000/mm^3$. In only one patient did the platelet count fall to $< 100,000/mm^3$. No problems related to wound healing were observed. All patients had complete alopecia, and no episodes of infection or stomatitis were observed. No drug-induced amenorrhea was documented in four menstruating females. Nonspecific and transient electrocardiographic changes occurred in two patients. Presently, no episodes of cardiomyopathy have been observed.

DISCUSSION

In recent years, various adjuvant treatments have been attempted in osteosarcoma following amputation or segmental resection in selected patients. None of the published reports have indicated the treatment of choice. However, available data show that encouraging results are being obtained with single-agent and combination chemotherapy

TABLE 1.—Summary of clinical data concerning 13 patients with classic osteogenic sarcoma

Patient No.	Age/sex	Primary tumor site	Type of amputation	No. of cycles of ADM/ % of optimal dose	Disease-free survival (mos)	Survival (mos)
1	12/F	Tibia	Above the knee	9/95	36+	36+
2	7/M	Radius	Above the elbow	7/100	33+	33+
3	34/F	Fibula	Above the knee	8/95	20+	20+
4	40/F	Femur	Subtrochanteric	8/100	16+	16+
5	13/F	Femur	Subtrochanteric	8/90	10+	10+
6	15/F	Femur	Subtrochanteric	7/100	7+	7+
7	10/M	Tibia	Above the knee	2/100	2+	2+
8	13/M	Tibia	Above the knee	7/100	32	33+
9	14/M	Humerus	Forequarter	6/100	21	25+
10	14/M	Ileum	Hemipelvectomy	8/100	18	20+
11	11/M	Tibia	Above the knee	6/100	8	16
12	12/M	Tibia	Above the knee	3/85	4	10
13	11/M	Femur	Subtrochanteric	1/100	1	6

(2–4,7). At this time, adjuvant immunotherapy alone does not seem to be effective in preventing the development of clinical metastases (8). The studies utilizing either ADM (4) or high-dose methotrexate (HD-MTX) (3) were those providing the first sound evidence of the real effectiveness of the combined treatment approach. The updated results of Wang et al (4) showed a 50% projected disease-free survival at 20 months after surgery in 21 patients treated with ADM alone (30 mg/m² for 3 consecutive days every 4 weeks). In their series, 13 of 21 patients were continuously free of disease for a period ranging from 5+ to 33+ months. The recent results from the Sidney Farber Cancer Institute (9) showed by life-table plot that 58% of 12 patients receiving vincristine-MTX-citrovorum factor and 70% of 22 patients treated with vincristine-MTX-citrovorum factor plus ADM were disease-free after 20 months. The survival by life-table plot at 4 years was 80% as compared to 16% for the historical control group. Sutow et al (2) utilized two multidrug regimens. The first combination (cyclophosphamide, vincristine, melphalan, and ADM, or CONPADRI-I) resulted in a 56% (24 of 43 patients) disease-free survival with a followup observation ranging from 12 to 61 months. The second treatment (cyclophosphamide, vincristine, melphalan, ADM, and HD-MTX, or COMPADRI-II) obtained a 67% (20 of 30 patients) disease-free survival with a followup observation ranging from 12 to 26 months.

In spite of the small number of patients suitable for analysis, our present series supports the evidence that adjuvant treatment with ADM is effective in prolonging the disease-free status in patients with "classic" osteogenic sarcoma. At present, published results fail to indicate that combination chemotherapy is definitely superior to single agents in the adjuvant treatment of osteosarcoma. However, the fact that the disease-free interval has been prolonged is probably not sufficient evidence to state, at this time, that the cure rate has been improved by the combined-modality approach. There is a possibility that adjuvant treatment only delays the appearance of new disease manifestations, as exemplified by the occurrence of some late metastases after the second year in our series as well as in that of Sutow (10). Only a long-term analysis will clarify this crucial point. On the basis of the above-mentioned considerations, we think that treatment with ADM is useful in the combined treatment approach for osteogenic sarcoma. The drug is undoubtedly effective in this tumor; it can be administered on an outpatient basis, and its toxicity is predictable and reversible provided the cumulative dose does not exceed 550–600 mg/m². On the basis of the initial findings reported by Frei and Jaffe (9), it seems logical and justified to attempt to include both MTX and ADM in the adjuvant treatment for operable osteosarcoma. The sequential administration of both drugs will allow more prolonged treatment since the total safe cumulative dose of ADM will be reached in a longer period of time. It is also conceivable that this type of sequential combination chemotherapy will prevent the occurrence of late relapses.

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Adjuvant Chemotherapy for Osteogenic Sarcoma

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SUMMARY

Twenty-nine evaluable patients with nonmetastatic osteosarcoma were given sequential combination chemotherapy utilizing high-dose methotrexate with citrovorum factor rescue, vincristine, adriamycin, and cyclophosphamide. Fourteen (48%) of 29 patients are currently disease-free for 8–48 months from initiation of chemotherapy with a median disease-free survival of 21 months. The projected 4-year disease-free survival is 13%. At 4 years the projected overall survival is 57%. In this particular study, adjuvant chemotherapy does not appear to significantly prevent the development of overt metastases. In four patients, delayed onset of metastasis was observed at 18–43 months from initiation of treatment.

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Over the past 2 decades there has been no substantial improvement in the survival or cure rate of osteogenic sarcoma following surgery, radiotherapy, or both (1). Most patients eventually succumb to metastatic disease. It has become evident that therapeutic modalities contemplated for this tumor should not only be aimed at controlling the primary tumor but also at eradicating metastatic disease. In the past, attempts at achieving long-term tumor control using various treatment regimens in the presence of overt metastatic disease have usually failed. Therefore, it would seem more logical to try to prevent the establishment of overt or gross metastases. Among the various methods tried so far in preventing the development of metastatic disease, the use of adjuvant chemotherapy has met with success in a variety of childhood malignancies (2–5). A similar approach applied to osteosarcoma appears worth exploring. The aim of adjuvant chemotherapy is destruction of micrometastases, prevention of clinical metastases, and achievement of cure rather than delaying the appearance of metastasis (6). The interest in using adjuvant chemotherapy in osteosarcoma has been enhanced by recent reports of the significant antitumor effect of high dose methotrexate (HDM) (7) and adriamycin (8) in the treatment of metastatic osteogenic sarcoma.

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In 1973, a study using adjuvant chemotherapy for osteosarcoma was initiated at Children's Hospital at Stanford and forms the basis of this report.

MATERIALS AND METHODS

During the period between January 1973 and December 1976, 33 patients with nonmetastatic osteogenic sarcoma were treated with adjuvant chemotherapy. The patients ranged in age from 5 to 20 years with a median of 13.5 years. Twenty-two were males and 11 were females. Except for one patient with parosteal osteosarcoma, all had classic osteosarcomas.

The location and types of treatment administered to the primary tumor are summarized in table 1. The surgical management in these patients varied since most patients were referred to us for chemotherapy following definitive surgical treatment of the primary tumor at other institutions. Radiotherapy was administered both to patients with unresectable primary tumors and to those who refused to have surgery. Irradiation with a concomitant radiosensitizing agent (9) was administered to three patients.

Prior to treatment, the absence of overt metastatic disease was established by bone scans, brain scans, and lung tomograms. Surveillance for metastatic disease consisted of monthly chest roentgenograms and bone and brain scans every 3 months. The median time from diagnosis to commencement of chemotherapy was 24 days with a range of 8–111

TABLE 1.—Location and treatment of primary tumor

Location	No. of patients	Surgery		Subradical surgery + radiotherapy	Radiotherapy
		Radical	Subradical		
Long bones					
Femur	12	6	5		1
Tibia	7	5	2		
Fibula	4	2	1	1	
Humerus	4	2	1		1*
Totals	27	15	9	1	2
Others					
Scapula	1				1*
Pelvis	3	1			2*
Vertebra	1				1
Maxilla	1			1	
Totals	6	1		1	4

*With concomitant radiosensitizer, BUdR.

days. Two to 3 weeks were commonly allowed for postoperative recovery.

The chemotherapy regimen consisted of a sequential combination of drugs utilizing HDM with citrovorum factor rescue, vincristine-adriamycin, and vincristine-cyclophosphamide (figs 1 and 2). Three-week rest intervals were allowed between courses of treatment. A complete cycle was repeated five times over a period of 1 year.

The initial dose of HDM was 100 mg/kg. This was increased by 100 mg/kg every 2 weeks to a maximum of 300 mg/kg, to test tolerance to the drug. Patients were subsequently maintained on the maximum dose.

Adequate renal and hepatic function were mandatory prior to HDM therapy. Vigorous oral or iv hydration and urine alkalinization were undertaken prior to and following HDM infusion. Plasma methotrexate levels were measured at 24, 48, and 72 hours following the completion of methotrexate infusion. More recently, adjustments in citrovorum factor rescue dosage were made according to a set of arbitrary guidelines (table 2).

RESULTS

A total of 33 consecutive patients were enrolled in the study. Two of the 33 were given chemotherapy by their referring physician beyond the period stipulated in the protocol and are therefore not evaluable. Two other patients have been in the study for < 1 month and are not eligible for evaluation. The results reported below refer to the remaining 29 patients.

Most patients tolerated full doses of HDM with minimal morbidity. In two patients the dose of methotrexate was reduced and maintained at 100–200 mg/kg because of repeated moderate-to-severe

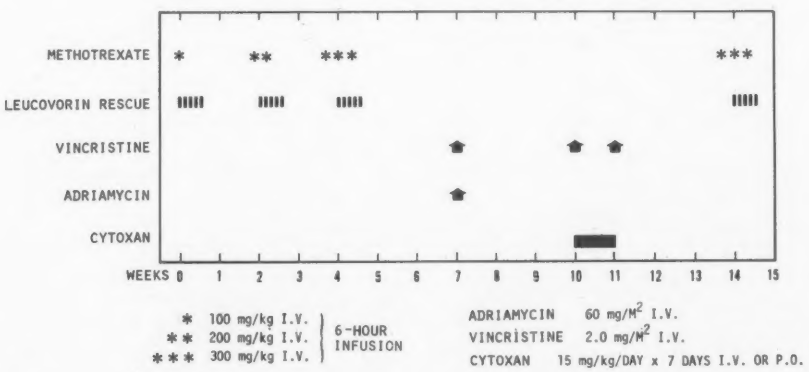
METHOTREXATE
LEUCOVORIN RESCUE
VINCRISTINE
ADRIAMYCIN
CYTOXAN
WEEKS 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
* 100 mg/kg I.V.
** 200 mg/kg I.V.
*** 300 mg/kg I.V.
6-HOUR INFUSION
ADRIAMYCIN 60 mg/M2 I.V.
VINCRISTINE 2.0 mg/M2 I.V.
CYTOXAN 15 mg/kg/DAY x 7 DAYS I.V. OR P.O.

FIGURE 1.—Adjuvant chemotherapy protocol for osteogenic sarcoma.

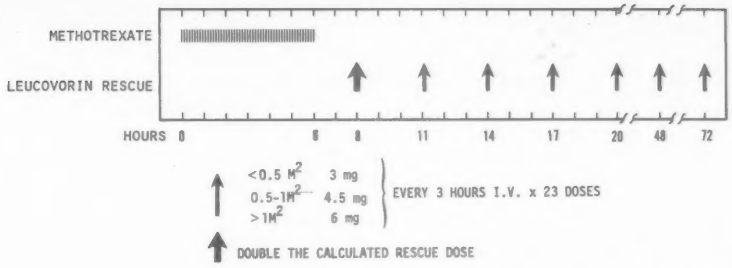

FIGURE 2.—HDM-citrovorum factor (leucovorin) rescue schedule.

gastrointestinal mucosal toxicity and myelosuppression. In a third patient, methotrexate was withheld temporarily because of decreased creatinine clearance. There were no deaths attributed to methotrexate toxicity.

Adriamycin was administered to all patients at full dosage with no major difficulties.

Many of the patients did not tolerate cyclophosphamide at 15 mg/kg for 7 days. The high incidence of prolonged profound neutropenia often associated with suspected or documented infections eventually led to the reduction of the cyclophosphamide dose to 10 mg/kg for 7 days.

The hematologic and clinical toxic effects observed with this chemotherapy regimen are summarized in tables 3 and 4.

Fourteen (48%) of 29 patients are currently disease-free for 8–48 months from initiation of chemotherapy with a median disease-free survival of 21 months. Nine of the 14 have completed 1 year of therapy.

Fifteen of 29 patients developed metastasis at 1–43 months following chemotherapy. In 11, metastatic disease occurred within 12 months of chemotherapy. Four patients developed delayed metastasis at 18, 21, 26, and 43 months from initiation of chemotherapy.

The lung was the initial site of metastasis in 13

TABLE 2.—Guidelines for modifying citrovorum factor rescue

Time (hrs) after HDM	Serum creatinine level	Plasma methotrexate levels	Citrovorum factor rescue
24	100% ↑ of baseline	Regardless of methotrexate levels	Continuous iv infusion at 10 times the standard citrovorum factor rescue dose
48	Normal	10^{-6} M	Continue standard citrovorum factor rescue until 72-hr levels are available
	50%–100% ↑ of baseline	10^{-6} M	Continuous iv infusion at 10 times the standard citrovorum factor rescue dose
	Normal	$< 5 \times 10^{-7}$ M	Stop citrovorum factor rescue after 72 hrs
72	Normal	$> 2 \times 10^{-7}$ M	Continue standard citrovorum factor rescue until methotrexate levels fall to safe levels
	50%–100% ↑ of baseline	$> 2 \times 10^{-7}$ M	Continuous iv infusion at 10 times the standard citrovorum factor rescue dose

patients while the bone was the site of initial tumor spread in only one. Another patient had local tumor recurrence of a primary maxillary tumor with subsequent intracranial extension.

Nine of 15 patients who developed metastatic disease died at 2–29 months from initiation of treatment. Four patients have subsequently been rendered disease-free following surgical resection or irradiation of metastatic disease with or without chemotherapy for 5, 8, 11, and 26 months from onset of metastatic disease.

At 4 years the projected overall survival in this group is 57% while the projected disease-free survival is only 13% (fig 3).

There was no significant difference in the incidence of metastasis between patients who had radical amputation and those who had nonradical amputation. Similarly, there was no correlation between time interval from diagnosis to initiation of chemotherapy and the incidence of metastasis.

DISCUSSION

In this study, adjuvant chemotherapy does not appear to significantly prevent the appearance of clinical metastasis. Most of those patients who developed metastasis manifested disease spread while receiving chemotherapy. One might speculate that in four patients chemotherapy may have delayed the appearance of metastasis; it is not known whether extending therapy beyond the 12 months would have prevented delayed metastasis in these four patients.

The overall survival probability in this group appears to be an improvement over that previously reported in the literature (1). However, the disease-free survival is unsatisfactory. Continued treatment

TABLE 3.—Incidence of hematologic toxic effects

Toxic effect	% of courses		
	HDM (142 courses)	Vincristine-adriamycin (88 courses)	Vincristine-cyclophosphamide (83 courses)
Anemia	9	10	22
Leukopenia	6	27	67
Thrombocytopenia	4	4	12

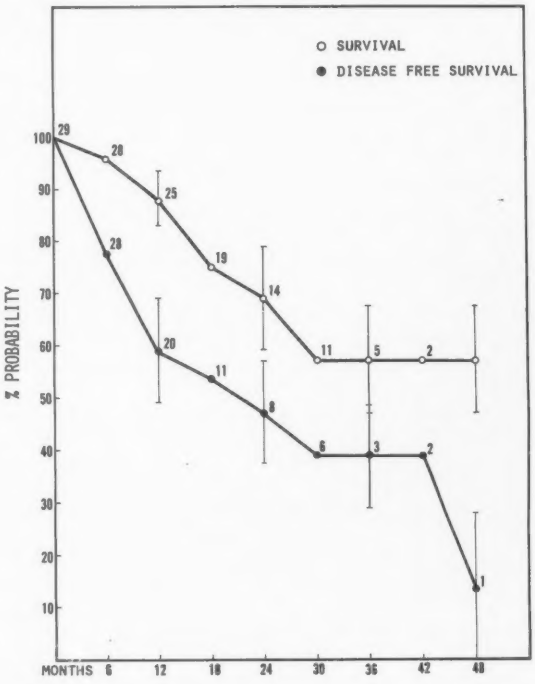

FIGURE 3.—Survival and disease-free survival probability from initiation of chemotherapy.

TABLE 4.—Incidence of clinical toxic effects

HDM-citrovorum factor rescue (143 courses)		Vincristine-adriamycin (88 courses)		Vincristine-cyclophosphamide (83 courses)	
Toxic effect	% of courses	Toxic effect	% of courses	Toxic effect	% of courses
Nausea/vomiting	119	Nausea/vomiting	31	Nausea/vomiting	46
↑ liver enzymes	62	Alopecia	88	Jaw pain	7
Mucositis	22	Jaw pain	4	Cystitis	7
Skin rash	8	Skin rash	5	Constipation	2
↓ creatinine clearance	4				
Infection	4	Infection	3	Infection	7
Candida esophagitis	1	Wound infection	1	Fever of unknown origin	6
Wound infection	3	Otitis media	2	Wound infection	1

of metastatic disease with surgery and radiotherapy, with or without chemotherapy, has contributed in part to the increased survival in these patients.

The lung remains the most common site of initial metastasis, suggesting that chemotherapy has not significantly altered the pattern of tumor spread in these patients.

Prevention of systemic disease spread remains a challenge in the treatment of osteosarcoma. To meet this challenge there is a continuous need to better understand the biologic nature of the osteosarcoma tumor cell and to search for other effective treatment modalities and chemotherapeutic agents that can be utilized in the treatment of this tumor.

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Adjuvant Therapy for Nonmetastatic Osteogenic Sarcoma: An Evaluation of Transfer Factor Versus Combination Chemotherapy [1]

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SUMMARY

A randomized study compared the effects of combination chemotherapy (high-dose methotrexate, adriamycin, and vincristine) with immunotherapy in the form of transfer factor in the adjuvant treatment of patients with nonmetastatic osteogenic sarcoma after apparent complete surgical ablation of the primary tumor. Thirty-two patients were evaluated. Of 22 patients who received chemotherapy, three died of drug-related complications and six were alive without disease recurrence between 260 and 673 days after operation. Ten patients in the transfer factor group converted their markers, and of these, five were alive without recurrence 420–753 days after operation. Neither treatment program was considered superior with respect to disease-free survival.

[Cancer Treat Rep 62: 289–294, 1978]

A number of reports have attested to the high incidence of pulmonary metastases in patients with osteogenic sarcoma after apparent complete surgical ablation of the primary tumor. The Mayo Clinic experience with 600 patients as reported in 1967 revealed a 5-year survival rate of 23% (1), which was consistent with the results of other large series as reviewed by Friedman and Carter (2) in 1972. Even though pretreatment studies revealed no evidence of pulmonary metastasis, this can be expected to become radiologically evident, with a mortality rate of 80% being related to metastatic disease. These observations have led to the conclusion that malignant cells have escaped to the systemic circulation before surgical ablation of the primary lesion, resulting in subclinical microscopic foci of metastatic involvement. One approach to this problem has been to irradiate the radiographically negative lung fields after amputation, but in our experience, this has not improved the disease-free survival figures (3).

Based on the reported antitumor activity of adriamycin (4) and high-dose methotrexate (5) in patients with metastatic osteogenic sarcoma, we incorporated these drugs into an adjuvant program for patients with osteogenic sarcoma whose primary lesion was surgically irradicable and who had no clinical or radiographic evidence of metastatic disease. Vincristine was added to the combination and administered before the methotrexate because of its apparent ability to promote uptake of methotrexate by tumor cells (6) and because of the reported therapeutic synergism that results from combination treatment with adriamycin in animal leukemia systems (7). Because we were concerned with presumed microscopic foci of disease, we postulated that the extremely high doses needed for treatment of metastatic disease would not be necessary for "prophylaxis." Thus, the program that was developed at the Mayo Clinic was designed to provide an effective chemotherapeutic regimen with tolerable toxicity that could be adapted to the particular needs of our patient population, many of whom have to travel long distances from their homes. The combination was subjected to pilot studies in adults with disseminated cancer and was well tolerated, thus making it suitable for use as adjuvant therapy in patients without overt evidence of metastatic osteogenic sarcoma.

Our other approach to adjuvant therapy for osteogenic sarcoma reflects our long-standing interest in cancer immunotherapy, and this was further stimulated by the many reports on the utilization of

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various immunotherapeutic procedures for the treatment of osteogenic sarcoma. Observations in the laboratory of tumor-specific reactivity by immunofluorescence and microtoxicity in a high percentage of patients with osteogenic sarcoma led us to the conclusion that patients who had survived and were apparently cured of their disease might yield specific transfer factor, although we have not been able to confirm that such transfer factor does, in fact, have osteogenic sarcoma specificity. Our interest in the use of transfer factor was further supported by the report of Levin et al (8) of apparent good results from the use of transfer factor in five patients with osteogenic sarcoma.

With this background and with the approval of the Mayo Clinic Human Studies Committee, a protocol study was designed that allowed for the randomization of patients with nonmetastatic "classic" osteogenic sarcoma to receive either transfer factor or combination chemotherapy after successful surgical removal of the primary tumor.

MATERIALS AND METHODS

Between July 1, 1974, and February 5, 1976, 36 patients with histologically confirmed operable classic osteogenic sarcoma of the bone without evidence of metastasis were entered in this study. During the same period, ten patients were not entered for randomization: two had parosteal osteogenic sarcoma, two had grade 1 lesions, one had Paget's disease, and one had the lesion located in the mandible; the other four were not eligible for randomization because of social, economic, and geographic reasons.

The preoperative evaluation included an immunologic profile, the details of which have been previously published (9). In addition to a general medical examination, patients eligible for the study had no abnormalities in whole-lung tomography and had normal liver, renal, and cardiac functions. Randomization was undertaken within 7 days of operation, and the patients were stratified according to their tumor histologic type because the Mayo Clinic experience to that date had suggested a somewhat worse prognosis for patients who had osteoblastic osteogenic sarcoma as compared with those who had other histologic types (1). Stratification was further dependent on whether the lesion was proximal or distal to the elbow or knee and on the response to delayed hypersensitivity skin testing (9).

The nature of the study was reviewed with patients and appropriate family members, and randomization to receive either combination chemotherapy or transfer factor was undertaken only after informed consent had been obtained and all aspects of the study had been discussed in detail. When all three stratification factors were considered, each patient was placed in one of eight strata, the definitions of which were based on histologic type, site, and skin test responsiveness, with random assignment within each of the eight strata.

Transfer factor was obtained from selected long-term survivors of osteogenic sarcoma who were disease-free in good health and had a strongly positive reaction to one of the skin tests utilized in the immunologic profile. Transfer factor was prepared from venous blood, as described by Lawrence and Al-Askari (10). Because we had previously observed depression of cellular reactivity during the first several days after surgical operation, transfer factor was administered after the 10th postoperative day, and 0.1 ml (which contains 1 unit of transfer factor in 10^9 lymphocytes) was administered sc; skin tests, which were previously negative, were repeated on both arms. If evidence of systemic transfer was present, that is, if skin test reactivity appeared on the arm contralateral to the transfer factor injection, no further therapy was administered and skin testing was repeated every 3 months thereafter. If there was no evidence of marker transfer, transfer factor from a new donor was selected, and a maximum of three new injections from three different donors was given; if there was still no evidence of adoptive transfer, the patient was crossed over to the chemotherapy arm of the protocol.

Followup studies in this group of patients included monthly chest roentgenograms and a complete physical examination every 3 months for the first 3 years, including whole-lung tomography and immunologic studies. The administration of transfer factor was repeated if, at the 3-month visits, the patient's marker reverted to negative.

The combination chemotherapy regimen (methotrexate, adriamycin, and vincristine [Oncovin] [MAO]) was instituted between the 15th and the 28th postoperative day in 20 patients and on the 39th day in the remaining two. Treatment was repeated every 4 weeks for a total of 12 treatments. Randomized patients received the three drugs as follows: vincristine, 1.4 mg/m² iv, followed by methotrexate at a dose of 2500 mg/m² as a 4-hour infusion, followed within 30 minutes of completion of the infusion by citrovorum factor (15 mg iv). Thereafter, citrovorum factor (12 mg) was given iv or im every 6 hours for 12 doses. Adriamycin was given iv at a dose of 40 mg/m² at 24 hours. The dose of adriamycin was increased or decreased by 10 mg/m² in subse-

TABLE 1.—Patients with osteogenic sarcoma

Lesion site	Operation	No. of patients: Total	With relapse	Without relapse	Drug death
Patients receiving transfer marker					
Converted marker					
Distal femur	Above-the-knee amputation	5	3	2	0
Distal femur	Hip disarticulation	1	1	0	0
Acetabulum	Hemipelvectomy	1	0	1	0
Proximal tibia	Above-the-knee amputation	3	1	2	0
Did not convert marker					
Distal femur	Above-the-knee amputation	1	0	1	0
Distal femur	Hip disarticulation	1	1	0	0
Ilium	Hemipelvectomy	1	1	0	0
Proximal femur	En bloc resection	1	1	0	0
Patients receiving combination chemotherapy					
Distal femur	Above-the-knee amputation	10	4	3*	3
Distal femur	Hip disarticulation	1	1	0	0
Proximal femur	Hemipelvectomy	1	1	0	0
Proximal femur	Hip disarticulation	2	0	2	0
Os calcis	Below-the-knee amputation	1	1†	0	0
Proximal tibia	Above-the-knee amputation	1	1	0	0
Proximal humerus	Forequarter amputation	2	2	0	0

*1 patient refused further chemotherapy after 1st course.
†Stopped after 9 courses; pulmonary metastasis 2 mos later.

quent courses, depending on interim toxicity. The maximal total dose of adriamycin was limited to 540 mg/m². Patients were hospitalized during the period of citrovorum factor rescue, and renal and hematologic functions were monitored. Before May 1976, serum methotrexate levels were not measured, but subsequently, these assays as well as a program of urine alkalinization were undertaken in all patients, and these patients remained hospitalized until the serum methotrexate level had decreased to 1×10^{-7} M.

Chest roentgenograms were obtained every 4 weeks before each course of treatment during the first year, every 2 months during the second year, and every 3 months thereafter. Whole-lung tomography and immunologic studies were repeated every 3 months.

Failure in either treatment arm was signified by evidence of tumor recurrence or metastasis, and all such failures were considered for further treatment. If the lesion was considered resectable, further surgery was performed. Patients who failed on transfer factor were crossed over to receive combination chemotherapy, and patients who had evidence of disease recurrence or metastasis while receiving combination chemotherapy were entered in the other chemotherapy protocol studies.

RESULTS

All 36 eligible patients were randomly assigned to treatment. Of the 18 patients assigned to the transfer factor arm, eight failed to convert their marker; of these, one chose to receive chemotherapy elsewhere, two refused crossover to combination chemotherapy, and one had a subsequent review that led to a change in diagnosis from osteogenic sarcoma to metastatic carcinoma of the pancreas. These four patients were, thus, excluded from analysis. Four other patients who failed to convert their marker were immediately crossed over to the MAO group. Thus, the final analysis consists of ten patients who received transfer factor and converted their marker, 18 who received MAO as primary therapy, and four who failed to convert their marker and were crossed over to receive combination chemotherapy. The details of site, type of operation, and outcome are included in table 1. This analysis includes observations up to December 31, 1976.

Of the ten patients who received transfer factor and converted their markers, five were alive and free of any disease 420–753 days after amputation. Five patients relapsed, four with pulmonary metastasis between 88 and 189 days after operation and one with recurrence of osteosarcoma in the stump 181 days after an above-the-knee amputation for disease in the distal femur. There was no morbidity associated with the administration of transfer factor.

Of the four patients who failed to convert after administration of transfer factor and were crossed over to receive combination chemotherapy, one was alive and free of disease 596 days after operation and three had recurrent disease, one with spinal metastasis 245 days after disarticulation for disease in the distal femur, one with metastatic disease in the contralateral pelvis and femur 349 days after en bloc resection for disease in the proximal femur, and one with pulmonary metastasis 147 days after hemipelvectomy for disease in the ilium.

Of the 18 patients assigned primarily to receive combination chemotherapy, five were alive without evidence of disease recurrence or metastatic disease between 260 and 673 days after operation. Three patients died of drug-related toxicity. Two deaths were related to methotrexate and occurred during the first and fourth courses. The third death (of cardiac failure) was related to adriamycin (cumulative dose of 500 mg/m^2) and occurred 274 days after operation. Autopsy in all three patients revealed no evidence of residual osteogenic sarcoma. Ten patients in this group have developed metastatic disease between 57 and 669 days postoperatively. Eight patients developed pulmonary metastasis, one developed pulmonary metastasis and disease in the hemipelvis after hip disarticulation, and one developed spinal metastasis. Only one of these patients completed 12 courses of treatment before recurrence, and in this instance, the patient was disease-free for 9 months after discontinuation of therapy. One patient refused further treatment after nine courses of chemotherapy and developed pulmonary nodules on Day 354, which was approximately 2 months after her last course of chemotherapy. A second patient refused further chemotherapy after experiencing life-threatening toxicity after his first course of treatment; he was still alive and disease-free 260 days after operation. In other patients, the number of courses of chemotherapy varied from one to ten, and in four patients, four or fewer courses of chemotherapy were administered.

In addition to the one patient who died of cardiac toxicity due to adriamycin, one other patient had electrocardiographic changes after nine courses of treatment, and the use of adriamycin was discontinued during the subsequent treatment cycles. Of the two patients who died of methotrexate-related toxicity, one (a 72-year-old woman) died 12 days after her first course of treatment and the second (a teenage girl) developed widespread gastrointestinal ulceration and pancytopenia after her fourth course of combination chemotherapy. Two other patients had moderately severe toxicity characterized by leukopenia and thrombocytopenia. Life-threatening infection and severe gastrointestinal ulceration developed in one patient in spite of monitoring serum methotrexate levels. These three patients recovered; one refused further treatment, and the others completed a total of seven and eight courses without further significant toxicity. A total of 155 courses of combination chemotherapy was administered.

Toxicity was tolerable in the remaining patients, with only 14 episodes of leukopenia (leukocyte counts $< 2500/mm^3$) and 20 episodes of thrombocytopenia (platelet counts $< 100{,}000/mm^3$). The adriamycin dose was increased in 14 patients, the highest single dose being 70 mg/m^2, and no increase in the initial dose of adriamycin was made in the remaining patients. Transient increases in levels of alkaline phosphatase, SGOT, and creatinine were noted in less than half the patients, but these values had returned to baseline levels before the next scheduled treatment. On one occasion, a persistent markedly elevated alkaline phosphatase level of bone origin was ultimately considered to be related to continued active osteosarcoma.

The incidence rates for metastasis and for death are shown in table 2.

DISCUSSION

The results of this study do not permit definite conclusions regarding the advantage of either of the two treatment programs in preventing the development of recurrent or metastatic osteogenic sarcoma. The metastasis rate is somewhat lower in the transfer factor patients who converted their markers, but the number of patients is too small to allow for any definite conclusions. The death rates as listed in table 2 showed no clear difference whether or not the drug-related deaths are included.

In comparing the results of this study with historical controls, it must be appreciated that improved methods of diagnosis and treatment may invalidate such comparisons. This is of particular significance when we analyze the results of treatment at the Mayo Clinic during the decade before institution of planned adjuvant therapy programs. The details of this analysis have been reported (11), but for purposes of comparison, figure 1 summarizes the re-

TABLE 2.—Rates of metastasis and death as of Dec 31, 1976, in patients with nonmetastatic osteogenic sarcoma

	Treatment group			
	Transfer factor (converted)	MAO + transfer factor crossed over to MAO	Started on MAO	Transfer factor crossed over to MAO
No. of patients entered	10	22	18	4
No. with metastasis	5	13	10	3
Mos exposed to risk	118.6	206.6	162.6	44.0
Rate/100 mos exposed	4.2	6.3	6.2	6.8
Deaths (total)	3	9	8	1
Mos exposed to risk	182.2	281.0	224.2	56.8
Rate/100 mos exposed	1.6	3.2	3.6	1.8
Deaths from disease	3	6	5	1
Mos exposed to risk	182.2	281.0	224.2	56.8
Rate/100 mos exposed	1.6	2.1	2.2	1.8

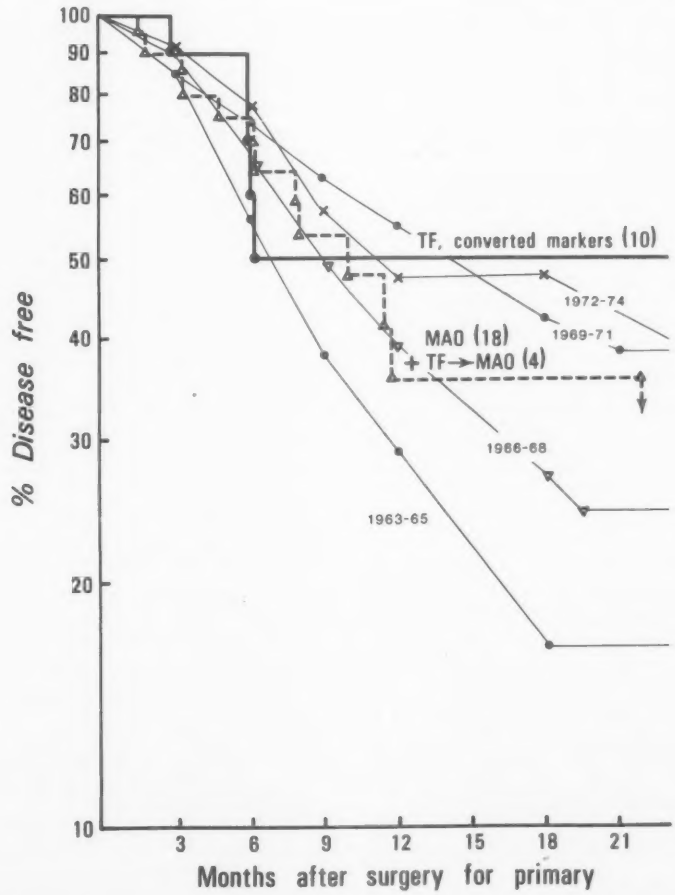

FIGURE 1.—% of patients still disease-free after surgery for primary lesion. Solid heavy line refers to the 10 patients who converted markers and who received only transfer factor as adjuvant therapy. Dashed heavy line refers to the 18 patients originally assigned to MAO group for treatment plus 4 patients assigned to transfer factor group who, on failing to convert markers, were transferred to MAO group. Underlying light lines are disease-free curves for historical data from the Mayo Clinic, 1963–1974.

sults of an analysis of disease-free survival for patients treated between 1963 and 1974 who either received no adjuvant therapy or received therapy subsequently considered to be ineffective and compares them with the results of the present study. With primary surgical treatment, there has been a progressive improvement in disease-free survival as compared with our own historical controls and those of Marcove et al (12). We cannot ascribe this change to any alterations in pathologic criteria because all the pathologic material at the Mayo Clinic has been personally reviewed by one pathologist and independently by pathologists from outside our institution. Changes in surgical technique do not seem to have a role, but earlier diagnosis and treatment in more recent years may have influenced the natural history of the disease. However, an analysis of these factors in terms of duration of symptoms before diagnosis and tumor size at the time of surgery does not support this hypothesis. There is reason to believe, however, that improved radiologic techniques, such as whole-lung tomography, allow for the earlier identification of metastatic foci and that some patients who in the past were considered to be free of metastasis at the time of amputation would be excluded from present-day programs. The inclusion of such patients in earlier studies tends to adversely influence the disease-free remission rates, while their exclusion would have the opposite effect in more recent studies. Finally, the possibility of a change in the natural history of osteogenic sarcoma related to changes in etiologic and host factors cannot be excluded.

Neither of the adjuvant treatment arms in the present study seems to be superior to the results of surgical treatment alone between 1969 and 1974, although a distinct advantage is noted when the results are compared with the results from patients treated between 1963 and 1965 and with our previously reported experience. Our results with combination chemotherapy seem to be less impressive than those reported by others (13–16) and this might be related to differences in dosage and treatment schedules. More recent reports, presented as part of this symposium, suggest, however, that this trend has not been sustained and that disease-free survival rates are beginning to approximate those observed at the Mayo Clinic, with or without benefit of adjuvant therapy. Thus, the question of the role of adjuvant chemotherapy must be evaluated in the light of these developments and must consider treatment-associated morbidity—both physical and psychologic—even if, as seems apparent, drug-induced mortality can be reduced by careful patient monitoring.

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Adjuvant Treatment of Osteogenic Sarcoma With High-Dose Cyclophosphamide

Margaret Shepp, Thomas F. Necheles,* Henry H. Banks, Won H. Oh, and Seymour Zimbler[1]

SUMMARY

Six patients with osteosarcoma and no evidence of metastases received postoperative adjuvant chemotherapy with high-dose cyclophosphamide (25 mg/kg iv every other day for five doses). Three of these patients are alive without evidence of disease at 2½, 3, and 5 years following diagnosis. The regimen was tolerable in terms of toxicity. Cyclophosphamide in high doses may be effective adjuvant therapy in some patients with osteosarcoma.

[Cancer Treat Rep 62:295–296, 1978]

Control of osteosarcoma by surgery and radiotherapy has been unsatisfactory. The long-term survival in most large series of osteosarcoma patients is poor because metastatic disease develops within months after surgery and radiation in most patients (1,2). Attempts to improve the survival of patients with metastatic disease have met with frustration since metastatic osteosarcoma has proved resistant to chemotherapy with most conventional agents. Recently, however, the development of effective adjuvant chemotherapy has improved the outlook for osteosarcoma patients (3,4).

Metastatic osteosarcoma is resistant to conventional doses of cyclophosphamide, but occasional responses to high doses of this agent have been reported (5). We had observed an objective partial response to cyclophosphamide in one patient with metastatic osteosarcoma. This led to the design of a protocol for the use of high-dose cyclophosphamide as adjuvant therapy for newly diagnosed osteosarcoma patients without evidence of metastases.

Cyclophosphamide, 25 mg/kg, was given iv every other day for five doses. The course of chemotherapy was repeated every 3 months until seven courses (18 months) were completed or until progressive disease occurred. The every-other-day schedule was chosen to allow rest from nausea and vomiting on alternate days. Dose reductions were not made for hematologic toxicity. Patients were hospitalized for the duration of each course of chemotherapy for management of nausea and vomiting and to provide iv hydration (3 liters/m²/day) to minimize the risk of hemorrhagic cystitis, which is a well-known complication of cyclophosphamide therapy.

Table 1 shows the characteristics of six patients who received postoperative adjuvant chemotherapy with cyclophosphamide. All of these patients had an amputation at a level above the involved bone shortly after diagnosis, and all were examined with chest roentgenography and lung tomography at the time of diagnosis and none had evidence of metastases. Chemotherapy was begun immediately after amputation and was continued for 18 months unless metastases developed. The current status of these patients is shown in table 1. Three patients developed pulmonary metastases while undergoing adjuvant therapy. They were subsequently treated with other cytotoxic agents, and two patients have died. Three other patients are alive without evidence of disease at 2½, 3, and 5 years from diagnosis, having completed their courses of adjuvant chemotherapy.

An additional patient, No. 7, underwent amputation for an osteosarcoma of the calcaneus in 1972. No chemotherapy was given at that time. He remained disease-free for 43 weeks after which a solitary metastatic pulmonary nodule developed; this was surgically resected, and high-dose cyclophosphamide was given for 18 months. He is still alive without evidence of disease for > 2 years following completion of chemotherapy.

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TABLE 1.—Adjuvant chemotherapy with cyclophosphamide for osteosarcoma

Patient No.	Diagnosis (yr)	No. of courses completed	Site of primary tumor	Metastases (wks from diagnosis)	Current status	Survival (wks)
1	1971	2	Femur	33	Died of disease	104
2	1971	1	Femur	34	Died of cardiomyopathy	252
3	1974	5	Tibia	62	Alive with disease	150+
4	1972	6	Femur	—	No evidence of disease	255+
5	1973	7	Femur	—	No evidence of disease	165+
6	1974	7	Fibula	—	No evidence of disease	155+
7	1972	7	Calcaneus	43 (*see* text)	No evidence of disease	258+

TOXICITY

The seven patients received a total of 35 courses of high-dose cyclophosphamide. Nausea and vomiting were universal and were only partially controlled by antiemetics. All patients experienced alopecia. Hemorrhagic cystitis did not occur, presumably due to the vigorous hydration which was given to the patients. Severe leukopenia occurred regularly after each course of therapy. The mean nadir of the wbc count was 1000/mm^3 with a range of 150–3500/mm^3. The nadir usually occurred 1 week after the last dose of cyclophosphamide and recovery of an adequate number of granulocytes usually occurred within another week. A patient's hematologic response to his first course of cyclophosphamide was a good prediction of his response to subsequent courses. Three febrile episodes occurred during periods of leukopenia; these were managed with antibiotics alone and recovery was prompt.

Most patients did not experience thrombocytopenia. When thrombocytopenia occurred, it was mild and was not associated with any bleeding. The lowest platelet count following chemotherapy was 50,000/mm^3 but most were > 100,000/mm^3. There were no deaths related to hematologic toxicity.

Cyclophosphamide in high doses is potentially cardiotoxic. No acute cardiotoxicity was seen in our patients and no cardiac disease developed subsequently, with one exception. This patient (No. 2) died of refractory congestive heart failure > 4 years after a single course of cyclophosphamide. She had also received the cardiotoxic drug adriamycin in a cumulative dose > 550 mg/m^2.

In summary, three of six osteosarcoma patients who received adjuvant chemotherapy with high-dose cyclophosphamide survive without evidence of disease. Another patient who received cyclophosphamide following resection of pulmonary metastatic disease has also become a long-term survivor. The number of patients treated in this series is small and we make no comparisons between cyclophosphamide and other agents for the treatment of osteosarcoma. We conclude only that cyclophosphamide, when given in high doses, may be effective adjuvant chemotherapy for osteosarcoma and we feel this drug merits inclusion in combination chemotherapy programs for this disease.

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Adjuvant Whole-Lung Radiation With or Without Adriamycin Treatment in Osteogenic Sarcoma

Eduardo Caceres,[1,*] Mayer Zaharia,[1] Manuel Moran,[1] and Francisco Tejada[2]

SUMMARY

Eighteen consecutive patients with osteogenic sarcoma were treated after initial surgery with 2000 rads of whole-lung radiation for 21–28 days. Eleven of these patients went on to receive adriamycin (20 mg/m² × 3 days every 6 weeks). Three of seven evaluable patients are free of disease in the radiation group (median time to recurrence, 130 days) while six of ten evaluable patients are free of disease in the radiation + adriamycin group (median time to recurrence, 310+ days). These results are similar to published experience with whole-lung radiation and adriamycin alone.

[Cancer Treat Rep 62:297–299, 1978]

Radiation to the lungs at the time of initial surgery in the primary treatment of osteogenic sarcoma may have postponed the appearance of lung metastasis in one study (1). Friedman and Carter (2), in a review of the treatment of osteogenic sarcoma, indicated the possible benefit of adjuvant chemotherapy with adriamycin or high-dose methotrexate with citrovorum factor. The value of adjuvant chemotherapy was later documented by Cortes et al (3) and Jaffe et al (4). These studies prompted us to evaluate the efficacy of postoperative whole-lung radiation with or without adriamycin in the treatment of patients with osteogenic sarcoma.

MATERIALS AND METHODS

Eighteen consecutive patients with the diagnosis of osteogenic sarcoma of the bone seen at the Instituto Nacional de Enfermedades Neoplasicas between September 1975 and October 1976 were treated with adjuvant whole-lung radiation with or without adriamycin. All patients received 2000 rads of whole-lung radiation from a cobalt source administered in 21–28 days of treatment immediately after primary surgical resection. Additionally, 11 of these patients received adriamycin at a dose of 20 mg/m² iv × 3 days repeated every 6 weeks to a total dose of 550 mg/m². Adriamycin was given to patients residing in metropolitan Lima.

All patients received either amputation or hemipelvectomy as their primary treatment and were followed every 4–6 weeks with chest roentgenogram, cbc count, and renal and liver function tests.

A followup evaluation was tabulated up to February 28, 1977. The disease-free interval was calculated from day of surgery to first evidence of relapse.

RESULTS

All seven patients treated with whole-lung radiation were considered evaluable. Ten of the 11 patients treated with whole-lung radiation and adriamycin were considered evaluable. One patient received two cycles of treatment with adriamycin in a very irregular schedule and was considered not evaluable. Both groups are similar with respect to sex, age, and site of primary tumor (table 1).

All patients who demonstrated recurrence of disease did so with metastasis in the lung. Three of seven patients in the radiotherapy group and six of ten patients in the radiotherapy + adriamycin group remain free of disease (table 1).

The median time to recurrence is 130 days for the radiation-treated group and > 310 days for the radiation + adriamycin group (fig 1). The survival

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TABLE 1.—Patient characteristics

	Treatment	
	Radiotherapy	Radiotherapy + adriamycin
No. of patients entered	7	11
No. of evaluable patients	7	10
Sex		
Female	3	2
Male	4	8
Age		
Mean	13.9	18.5
Range	11–19	11–25
Primary tumor		
Femur	3	6
Tibia	4	4
No. of patients free of disease	3	6

rate at 18 months is 53% for the radiotherapy group and 80% for the radiation + adriamycin group (fig 2).

No side effects from the whole-lung radiation or adriamycin treatment have been noticed except for moderate leukopenia and thrombocytopenia in the adriamycin-treated patients.

DISCUSSION

In a recent study, Rab and associates (5) were unable to demonstrate any value for the use of pulmonary irradiation at the time of primary treatment of patients with osteogenic sarcoma. This report shows similar experience with the use of whole-lung radiation. Similarly, the use of whole-lung radiation followed by adriamycin did not decrease any further the incidence of recurrence as compared to published results with adjuvant adria-

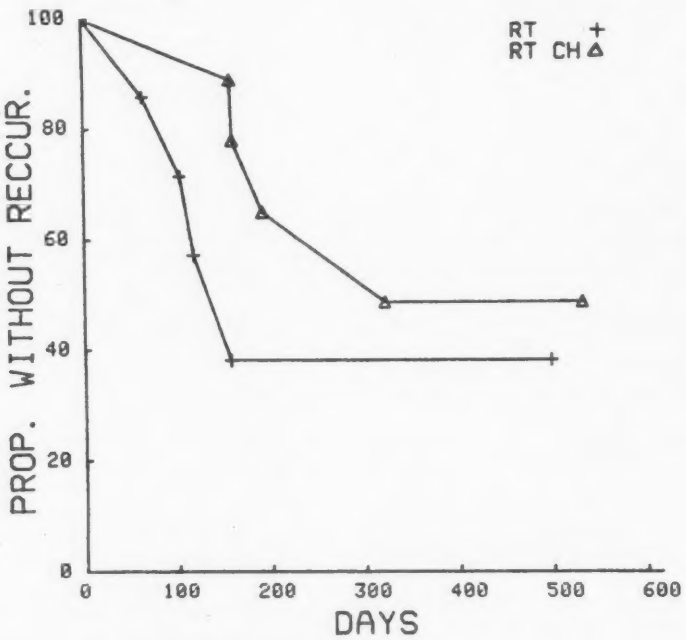

FIGURE 1.—Disease-free interval in patients with osteogenic sarcoma. RT = radiotherapy alone; RTCH = radiation + adriamycin.

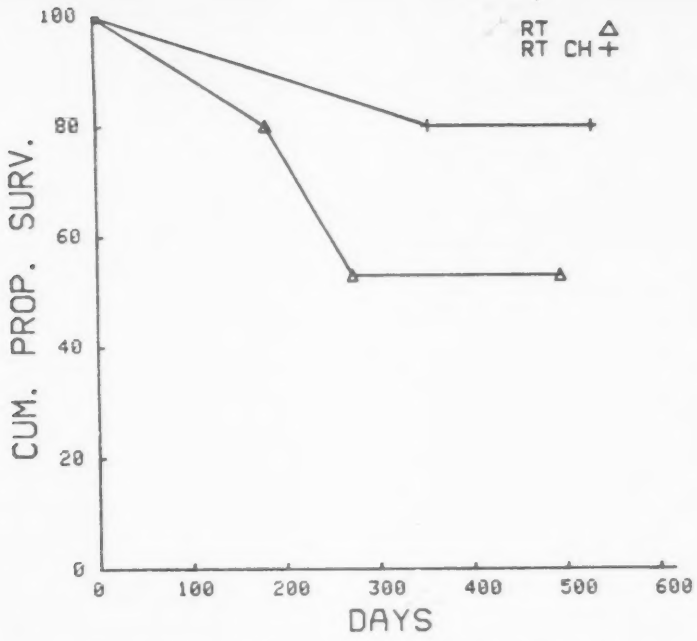

FIGURE 2.—Survival time in patients with osteogenic sarcoma.

mycin treatment (3). Therefore, whole-lung radiation was not found to be of value in the adjuvant treatment of osteogenic sarcoma as compared to Rab's study and the addition of adriamycin to whole-lung radiation did not improve the results over and above the results already published with adriamycin treatment alone.

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Five Years of Adjuvant Treatment of Osteosarcoma: More Questions Than Answers

Franco M. Muggia* and Arthur C. Louie[1]

The adjuvant treatment of osteosarcoma, which was hailed as a landmark when initially reported, has produced extensive repercussions (1). Many trials in other malignant conditions were stimulated by the reports of successful chemotherapy following primary surgical treatment of osteosarcoma. In addition, the enormous interest generated in the management of these patients has replaced the lack of enthusiasm which existed for many years. For example, the multidisciplinary teams created in many hospitals have carefully examined improved methods, not only for the initial amputation, but also for new surgical approaches and aggressive combined treatments of pulmonary metastases. Finally, increasing delineation of prognostic variables has been acquired through adequate input from statistical scientists, pathologists, and clinical oncologists.

The reports in this issue bring together the many ripples that emanated from the initial optimism, but they show a wide disparity of opinion on the fate of adjuvant treatment. In fact, the assessment of data from adjuvant trials ranges from unbridled optimism, to cautious noncommittal reporting, to outright pessimism. Unraveling the true therapeutic value of adjuvant chemotherapy in these studies may be an impossibility because of the many internal differences in study design, the number of prognostic variables associated with osteosarcoma, and the low rates at which single institutions and groups accrue patients with this relatively rare disease. However, we shall attempt to critically identify and analyze the therapeutic accomplishments of the last 5 years, as described in the reports published in this volume. For this purpose, we shall comment on the contributions covered in each section of the conference of January 1977 and updated in the respective articles.

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Prognostic Factors and Design of Trials

All contributions recognize the variable course of osteosarcoma from various sites, but reporting of data for other clinical and pathologic variables is less consistent. However, it is a healthy sign that, compared to similar past studies, the current studies are more careful in stating and describing prognostic factors.

To achieve more homogeneity, comparison of results limited to femoral lesions of the "classic" histologic variety is likely to be more informative than one including tumors from all sites. We have attempted to do this in Table 1 by compiling results limited to femoral lesions, where such cases could be separated from the main body of patients in the adjuvant studies presented in this issue. Further discussion of these cases will be made in a later section on adjuvant studies. Unfortunately, because of the relative rarity of this disease, most series, including several of the contributions presented here, analyze the entire patient group without further breakdown by tumor site.

Figure 1 summarizes the prognostic variables which might be considered important in stratifying patients and analyzing future trials. The desirability of including a specific stratification variable would depend on a number of factors. However, full analysis should include a description of the prognostic variables. The actual time of entry into the study should not be neglected; if too long a period elapses, a preselection of a more favorable group is inevitable.

Finally, the issue of using historical controls in determining survival differences must be faced squarely. It is evident that matching of prognostic variables cannot account for changes in the assessment of patients, in surgical techniques, and in the overall management of the disease upon recurrence, all of which have occurred with the passage of time. Therefore, comparing current data versus historical controls will remain suspect, notwithstanding that the experiences reported are likely to be global (ie, including all patients at one institution, which reduces the likelihood of preselection bias).

TABLE 1.—Osteosarcoma: adjuvant studies in femoral lesions*

Investigator	No. of patients entered	Type of surgery	Adjuvant treatment†	No. of patients with no evidence of disease (time)	No. of deaths (time)
			Surgery followed by adjuvant chemotherapy		
Cortes, Holland, Glidewell	47	Amputation	ADR, 30 mg/m²/day × 3, q4–6wks up to 540 mg/m²	26‡	?
Pratt, Rivera, Shanks, et al	14	Amputation§	ADR, 25 mg/m² iv Days 1 and 2; CTX, 600 mg/m² iv Day 3; HDMTX, 100 mg/kg 6-hr infusion, on Day 14 CF rescue	7 (23–48 mos)	6¶
Gilchrist, Ivins, Ritts, et al	9	AK amputation,** hip disarticulation	Transfer factor (TF) 0.1 ml sc, 1 unit TF in 10^9 lymphocytes (6 of 9 converted immunologic reactivity on TF)	2 (420–753+ days); 1 failed to convert, was crossed over to CTX, and has no evidence of disease at 596 days	?
	14		"MAO" q7wks × 12: MTX, 2500 mg/m² 4-hr infusion, CF rescue; ADR, 40 mg/m² iv; VCR, 1.4 mg/m² iv	6 (260–673 days)	?
Bellani, Gasparini, Gennari, et al	4	Amputation	ADR, 75 mg/m² iv q4wks × 6–8 mos up to 600 mg/m²	3 (16+, 10+, 7+ mos)	1 (8 mos)
Shepp, Necheles, Banks, et al	4	Amputation	CTX, 25 mg/kg iv qod × 5 doses q3mos × 7	2 (255+, 165+ wks)	2 (104, 252 wks)††
			Preoperative chemotherapy, local en bloc resection, and postoperative adjuvant chemotherapy		
Marcove	17	Local en bloc resection	Preoperative VCR-HDMTX-CF-ADR; postoperative CTX-VCR-HDMTX-CF-ADR × 5 cycles	9 (2–35+ mos)	8
Jaffe, Watts, Fellows, et al	2		Preoperative VCR-HDMTX-CF × 8 courses; postoperative VCR-HDMTX-CF-ADR	1 (9 mos)	0
	3	Local en bloc resection	Preoperative VCR-HDMTX-CF (8, 2, 8 courses) + intra-arterial ADR (75, 45, 75 mg/m²) Postoperative VCR-HDMTX-CF-ADR	3 (6+, 5+, 1+ mos)	0

*All patients had negative metastatic workups at entry.

†CTX = cyclophosphamide; HDMTX = high-dose methotrexate; VCR = vincristine; CF = citrovorum factor; ADR = adriamycin.

‡Includes 8 of 18 patients in the no protocol violation group and 18 of 29 in the protocol violation group.

§Includes 1 patient with hemipelvectomy for a femoral neck lesion.

¶Includes 1 patient dead from MTX toxicity.

**Transfer factor treated patients: 6 of 9 AK amputations + 2 of 9 hip disarticulations + 1 of 9 en bloc resections. "MAO" (MTX + ADR + VCR) treated patients: 10 of 14 AK amputations + 3 of 14 hip disarticulations + 1 of 14 hemipelvectomies.

††1 patient died of progressive disease at 104 wks; the other died of cardiomyopathy (congestive heart failure) following treatment with ADR.

Surgical Treatment

The four papers in the surgical treatment section of this issue discuss approaches taken at each of the respective institutions. As a group, these papers show that surgical techniques for the treatment of osteosarcoma have improved in recent years. In particular, new techniques being developed for orthopedic reconstruction may allow restoration of bone and joint function following radical en bloc resections. For particular groups of patients having tumors of the proper location and size with minimal

Pathologic type

Site
- Proximal vs distal
- Face and jaw lesions
- Skull and vertebral lesions

Age

Sex

Tumor size

Degree of metastatic workup

Interval between onset of symptoms and presentation for treatment (rate of growth)

Patient referral patterns

Presence of osteosarcomas of known cause
- Paget's disease-induced osteosarcomas
- Radiation-induced osteosarcomas

Interval between time of surgery and time of entry into study

FIGURE 1.—Prognostic variables in osteosarcoma (*from* refs 4 and 5).

soft tissue involvement, these developments raise the possibility of successful limb preservation despite aggressive treatment of the tumor.

At this point a word of caution is necessary. Any change in surgical therapy will complicate interpretation of future trials, particularly adjuvant trials, unless steps are taken to insure adequate separation of the different surgical groups. Careful analysis of local effects should be part of any evaluation of these new techniques; this refers not only to assessing the rate of local recurrence but also to assessing the eventual functional outcome. While exploring these new therapies, one must not lose sight of the ingredients of surgical judgment, ie, what objective tests can be used to determine the actual line of resection and what operative findings allow one to carry out procedures other than amputation.

Another approach described in this group of papers (papers by Eilber and Jaffe) is the use of preoperative chemotherapy and radiotherapy. The preliminary experience, though encouraging and indicative of great potential for similar multimodality approaches, is still very limited and indicates the need for caution in subsequent trials. We would suggest that future trials of a similar nature be attempted only by very experienced teams giving close attention to assessing the risk of local and metastatic recurrence.

Chemotherapy

A striking feature of this group of studies is the relative paucity of observations in advanced disease relative to the adjuvant experience. Dr. Pratt's paper (this issue) estimates that three fifths of the osteosarcoma patients admitted to his institution are eligible for adjuvant treatment. The other patients have disease that is metastatic, multifocal, or relatively inaccessible to surgery. It is somewhat surprising that this latter group is the subject of so few clinical trials. However, wide acceptance of attempts at resection of metastases lessens the opportunity for trials in measurable disease.

A second issue of great importance to clinicians pertains to the relative value of high-dose methotrexate (MTX) as opposed to adriamycin (ADR). There are no data available to answer this question. High-dose MTX itself remains somewhat of a mystery because of the lack of experience. Jaffe et al (2) have indicated improved results in adjuvant as well as metastatic treatment with more frequent courses of high-dose MTX. Could suboptimal drug schedules explain the variable results achieved in other trials using high-dose MTX? Although this would be a convenient explanation, confirmatory evidence is quite scanty. What about the question of the relative efficacy of high-dose versus low-dose and moderate-dose versus low-dose MTX? Again, there are no data. One study by the Children's Cancer Study Group (fig 2) will attempt to answer the question of high-dose versus moderate-dose MTX. However, both arms of the study include adriamycin and are mainly addressed to the surgical adjuvant situation. In addition, the widely spaced treatment schedule

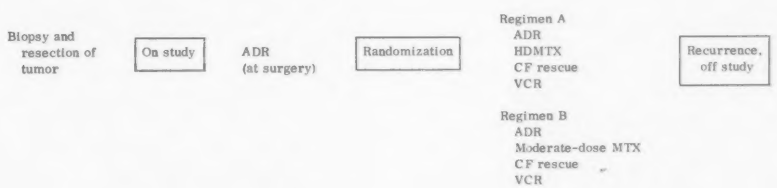

FIGURE 2.—Children's Cancer Study Group study 741: osteogenic sarcoma, primary and metastatic disease (*see* table 1 for drug abbreviations).

does not indicate how more frequent schedules would fare. Answers to all of these questions are obviously pressing.

Another area requiring attention is an assessment of the responsiveness of primary lesions to "local" therapies, including intra-arterial chemotherapy to the involved limb and systemic chemotherapy with and without local radiotherapy. Although the experiences of Eilber and Jaffe indicate local tumor sensitivity to preoperative chemotherapy, additional critical analysis is needed. Perhaps angiographic studies coupled with other diagnostic and pathologic studies may be helpful. The interaction between chemotherapy and radiotherapy also requires more intensive scrutiny.

In summary, chemotherapy has shown some effectiveness in osteosarcoma but the data are surprisingly scarce. In addition, there is a great need to develop additional experience with chemotherapy for metastatic osteosarcoma.

Adjuvant Studies

Osteosarcoma adjuvant studies have been responsible for stimulating new areas of knowledge and new approaches in therapy. Many of the ingredients in the design and execution of these studies have been covered. It should be evident that firm conclusions cannot be reached because of the many factors influencing the course of the disease. In fact, these studies have produced many more questions than answers.

Believing that an analysis of results from therapeutic trials limited to one site is probably more informative than interpreting data from all sites, we compiled table 1 listing results from adjuvant trials limited to femoral lesions. The data are derived from the adjuvant studies presented in this issue. We were able to select patients with femoral lesions from seven of the ten adjuvant studies. Five of those studies are straightforward adjuvant studies, while the other two utilize preoperative combination chemotherapy followed by local en bloc resection and postoperative combination chemotherapy.

The five adjuvant studies can be further divided into those that use ADR alone, high-dose cyclophosphamide alone, and combination chemotherapy incorporating both ADR and/or high-dose MTX and other agents (table 1). When the regimens are compared for percentage of patients living free of disease, it is striking that single-agent ADR produces results essentially identical to combination regimens that add high-dose MTX and other agents to ADR. Of course, this analysis is incomplete since we were unable to include data from the studies of Jaffe, Etcubanas and Wilbur, and the Southwest Oncology Group, because in each case the subgroup of patients with femoral lesions could not be separated from those with lesions at other sites.

The two studies that use preoperative chemotherapy, local en bloc resection, and postoperative adjuvant chemotherapy, when combined, appear to give results slightly better than those achieved by adjuvant therapy alone. However, both studies report early results and the number of patients involved is small and followup time is relatively short.

Although our analysis is based on an incomplete sampling of the data, we feel that it is important to begin looking at the data in this way. Although firm conclusions cannot be made, our exercise will have been a useful one if future studies begin reporting data by specific tumor site and type of surgical treatment.

A very striking feature in all reported adjuvant trials is the complete lack of untreated controls. This has always been justified by comparing the 50%–60% survival rate of treated groups against the dismal 20% survival rate of untreated historical controls. In unpublished data of the Mayo Clinic there is evidence that osteosarcoma patients, comparable to those included in adjuvant trials, have a 2-year disease-free survival of 40%–45% in the absence of adjuvant treatment. This finding, if verified by other groups, would invalidate the use of historical controls from the recent past and would require re-evaluation of all adjuvant treatment regimens. In fact, a study at the Mayo Clinic (fig 3) has been initiated to answer this question.

Another question raised by adjuvant studies is whether the variability of the chemotherapy regimens accounts for the moderate variability of results. Although other factors such as patient selection may be as important in influencing results, this factor cannot be excluded without gaining more experience with chemotherapy in advanced disease.

DISCUSSION

We subtitled this summary "More Questions Than Answers" because at the end of the conference many important questions remained which were only just beginning to be answered. For example, it would be very useful to know whether chemotherapy alters the pattern of recurrences, as is suggested in some trials but not in others. Jaffe's initial series has continued to indicate recurrences which are very late and unexpected. Similar changes in the timing and pattern of recurrences have been reported by Sutow (3) but other experience (by Etcubanas) suggests no changes in the pattern of recurrences. An altered pattern of recurrences may, in itself, be important in facilitating subsequent

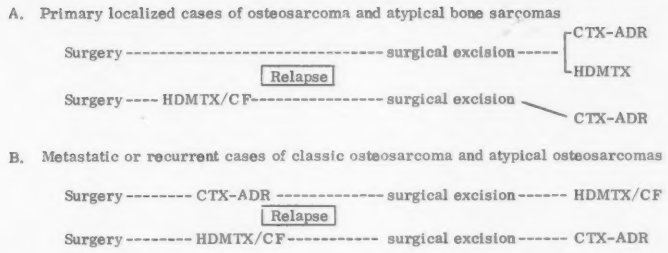

FIGURE 3.—Mayo Clinic study 76-76-01: a prospective randomized study of postsurgical adjuvant therapy for osteogenic sarcoma (*see* table 1 for drug abbreviations).

treatment which may result in prolonged survival.

Is the improvement in survival rate related to the above phenomenon or only to the more aggressive approach to metastases? This is perhaps the most crucial question. It is this feature that renders the Mayo Clinic trial with an observation arm so important. If it can be demonstrated that equally good results in metastatic disease, once it develops, may be obtained by aggressive surgery and chemotherapy, then many patients can be spared the intensive adjuvant treatment. Alternatively, demonstration of an altered pattern of recurrences would represent an important biologic fact which would strengthen the validity of current approaches and produce a new perspective.

We need to know what the optimal surgical procedure and preoperative approach should be. This is an area in great flux at this time. As we have seen, the trend is toward limb-saving surgical procedures for particular groups of patients. Also, there is some evidence for the efficacy of preoperative chemotherapy. Whether these approaches will be successful depends largely upon gathering comparable data from different institutions.

One of the most educational aspects of the papers in this issue lies in asking why there is such a divergence of viewpoints with data that are essentially not dissimilar. Clinical trial methodology and reporting are fraught with pitfalls, and theories must eventually give way to facts. Exclusions, for reasons such as protocol violations, and comparison with historical controls may follow the theoretic concepts of the investigators. Conflicting experience can have many origins, but at least one possibility is that the exclusion or comparison was not strictly valid. When this occurs, it is absolutely important to expand the data base and scrutinize the results through clinical trials that are preferably randomized to the appropriate questions.

It would be too harsh to conclude that progress in the treatment of osteosarcoma lies in the eyes of the beholder. However, it is important to consolidate the advances made in the management of these patients by carefully scrutinizing conflicting issues and developing additional experience in carefully designed and evaluated therapeutic trials. This may be possible in most instances only through cooperative ventures evaluating no more than two therapeutic alternatives.

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Studies With High-Dose Methotrexate—Historical Background

Abraham Goldin [1,*]

Since their initial synthesis some 40 years ago, the folic acid antagonists have been subjected to extensive investigations both in the laboratory and in the clinic, and methotrexate (MTX) in particular has found broad usage in the treatment of hematologic malignancies and solid tumors. In studies with the folic acid antagonists it was demonstrated that the therapeutic activity of an antitumor agent is not a fixed property, but that it may be manipulated by appropriate alteration of the manner in which the drug is employed. Both experimental and clinical investigations have shown that the dose and schedule of administration may have a profound influence on therapeutic efficacy. Furthermore, the choice of optimal scheduling can be influenced by the extent and location of the neoplastic disease at the time when treatment is initiated, as well as by various pharmacologic factors relating to the host-tumor-drug relationship. Goldin et al (1) and Skipper et al (2) have demonstrated that the ability of MTX to totally eradicate a tumor cell population is related to the dosage of drug that can be employed. A linear relationship was observed between the MTX dose and the size of the leukemic cell population that could be totally eradicated (1). Further, with both aminopterin and MTX the total dose of drug employed could be manipulated by the use of citrovorum factor (CF). The interest in the attainment of a high-dose therapy program for osteogenic sarcoma makes an historical review of experimental studies of high-dose MTX of pertinence to this symposium.

The history of high-dose MTX has as its basis a series of studies with aminopterin. Aminopterin and MTX were synthesized by Seeger et al in 1947 (3) and 1949 (4) respectively. Great interest was created in the antifolics by the demonstration of Farber et al (5) in 1948 that aminopterin was capable of producing temporary remissions in acute leukemia in children.

Prior to our initiation of studies with the antifolics, various folic acid antagonists had been prepared by Smith et al (6), and some of them appeared to have an inhibitory effect on neoplastic growth.

Our initial interest in the antifolics dates back to 1949 when we reported that aminopterin retarded the growth of transplanted Sarcoma 180 in mice (7). The extent of inhibition increased with increasing dosage.

Seeger et al (3) and Oleson et al (8), employing *Streptococcus faecalis* as the test organism, obtained inhibition of growth by aminopterin and reversal of this inhibition by pteroylglutamic acid (folic acid). Franklin et al (9) obtained some indication of reversal of the aminopterin effect on the growth and survival of mice by administration of folic acid in feeding experiments. In the rat and the chick, Oleson et al (8) demonstrated that very high levels of folic acid gave a partial reversal of growth inhibition.

In 1949 (10), we demonstrated that folic acid was capable of reversing aminopterin-induced inhibition of Sarcoma 180. In the same year, Burchenal et al (11) demonstrated interference with the antileukemic effectiveness of MTX by administration of folic acid. In 1950, they observed prevention of the antileukemic action of MTX on treatment with CF (12). In the Sarcoma 180 studies (10), the mice were injected iv for a total of 4–6 days, treatment being initiated 1 day after implantation of the tumors. In groups where the mice received injections of aminopterin and folic acid, the order of injection was alternated at each injection period, so that aminopterin was injected first on 1 day and folic acid was injected first on the second day, with an interval of 1 hour between each of the injections. Although only partial reversal was observed on this schedule, in additional studies complete reversal of the inhibition of Sarcoma 180 was observed when the injections of folic acid were begun 1 day prior to the administration of the aminopterin (ie, 25 mg/kg of folic acid and 0.3 mg/kg of aminopterin). At high doses of folic acid (50 mg/kg) there was some indication of inhibition of tumor growth by the folic acid itself.

There was somewhat erratic behavior with respect to reversal of antitumor activity in the various experiments. There was some indication that the scheduling of folic acid relative to aminopterin could be critical. Attention was therefore turned to stud-

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TABLE 1.—Temporal relationships in protection against folic acid antagonist (aminopterin) toxicity to mice (*from* refs 13,21)

Time of administration of folic acid or CF relative to aminopterin (hrs)	% survival from aminopterin toxicity*		
	Folic acid (25 mg/kg)	CF (mg/kg)	
		75	53.25
-24	50	100	30
-12	60		
-8	70		
-3	70		
-1	100	100	100
0	10	100	
+1	20	100	100
+3	0		
Aminopterin alone (10 mg/kg)	10	10	

*10 mice/group.

ies involving scheduling of therapy for aminopterin and folic acid, using lethal toxicity to the mice as an endpoint. In 1950 (13), we reported studies on the requirements for the prevention of aminopterin toxicity by folic acid in mice. In this study an optimal time interval for the demonstration of protection against lethal toxicity by the administration of folic acid was established as 1 hour prior to the antagonist (table 1). Simultaneous or subsequent administration of folic acid failed to prevent toxicity of the antagonist. Protection from supra-lethal doses of aminopterin was obtained repeatedly at weekly intervals, but no protection could be obtained by the daily administration of the metabolite and antagonist even when the folic acid was given 1 hour prior to the aminopterin at each instance.

In 1950, Schoenbach et al (14) reported on the reversal of aminopterin and MTX toxicity in patients by CF.

By 1951, interest in the mechanism of action of the folic acid antagonist aminopterin was engendered by an increasing number of clinical reports of its therapeutic efficacy in patients with acute leukemia (5,15–18), and it was quite clear that with aminopterin and other antifolates, the therapeutic efficacy was hampered by the serious toxic reactions that were induced in man. Our demonstration of protection by folic acid administered 1 hour early with respect to aminopterin against drug toxicity stimulated our interest in studies with CF. In 1950, Nichol and Welch (19) provided a demonstration of the conversion of folic acid to CF in rat liver slices. They had also observed protection of rats from aminopterin-induced toxicity on administration of CF (20). In 1951 (21), we reported that CF could afford complete protection when administered either 1 hour prior to, concomitantly with, or 1 hour subsequent to the administration of a toxic dose of aminopterin (table 1).

In 1952, we reported a detailed series of studies on the biologic inter-relationships of folic acid, CF, and the antimetabolite, aminopterin (22). A linear relationship was observed between the median lethal dose of aminopterin (LD50) for mice and the dose of folic acid administered 1 hour prior to the aminopterin (table 2) (22). However, no such relationship was observed on simultaneous administration of the drugs.

In contrast, on simultaneous administration of CF with aminopterin, a linear relationship was observed between the LD50 of aminopterin and the dose of CF employed (table 2) (22).

After pretreatment with a sub-LD50 dose of aminopterin (0.1 mg/kg, 1 day early), folic acid administered 1 hour prior to aminopterin did not result in any significant increase in the LD50 compared with corresponding pretreated groups that were subsequently treated with aminopterin alone (table 3) (22).

Similarly, after pretreatment with folic acid 1 hour early (25 mg/kg FA^{-1}) plus aminopterin (0.1 mg/kg), there was no protection afforded the next day (Day 1) by 25 mg/kg FA^{-1} plus aminopterin. A similar result was also obtained on pretreatment with CF and aminopterin, followed the next day by treatment with FA^{-1} plus aminopterin.

In contrast, following similar pretreatment with aminopterin, treatment with simultaneous CF plus aminopterin 1 day later did result in significant increases in the LD50 (table 3). Similar increases in the LD50 were observed on pretreatment with FA^{-1} or CF^{-1} or CF^{0} plus aminopterin. However, with the low dose of CF employed (7.5 mg/kg), there was a diminution in protection, since the pretreatment dose with aminopterin approached the LD50 dose of aminopterin alone.

With a fixed dose of CF (7.5 mg/kg), there was a progressive decline in the LD50 of aminopterin as

TABLE 2.—Competitive (linear) relationship of folic acid and CF at optimal time of administration to the toxicity of aminopterin (*from* ref 22)

Folic acid given 1 hr prior to aminopterin		CF given concomitantly with aminopterin	
Folic acid (mg/kg)	Aminopterin LD50 (mg/kg)	CF (mg/kg)	Aminopterin LD50 (mg/kg)
0	4.1	0	4.9
2.5	6.8	0.75	8.0
5	11.0	1.88	11.2
15	22.1	3.75	15.8
25	33.1	7.5	24.7

TABLE 3.—Effect of pretreatment with aminopterin on the subsequent protection afforded by folic acid or CF against aminopterin toxicity (*from* ref 22)

Pretreatment on Day 0 with aminopterin (mg/kg)	Treatment on Day 1 with—			
	Folic acid* (mg/kg)	Aminopterin LD50 (mg/kg)	CF† (mg/kg)	Aminopterin LD50 (mg/kg)
0	0	5	0	4
0	25	26	7.5	26
0.01	0	4	—	—
0.01	25	18	—	—
0.1	0	4.3	0	3.5
0.1	25	3.5	7.5	24
1.0	0	1	0	1.0
1.0	25	1	7.5	18
2.0			0	0.5
2.0			7.5	14
4.0			0	0.5
4.0			7.5	3

*Folic acid administered 1 hr prior to aminopterin on Day 1.
†CF administered simultaneously with aminopterin on Day 1.

the administration of CF was withheld for longer periods of time (table 4) (22). However, a tenfold increase in the dose of CF (75 mg/kg) administered 24 hours after the administration of aminopterin resulted in a significant increase in the observed protection (LD50, 17 mg/kg) compared with the result obtained with administration of 7.5 mg/kg of CF (table 4) (22). However, with the high dose of CF (75 mg/kg) administered 48 hours after aminopterin, no significant increase in protection was observed.

Prior to the observation that aminopterin and MTX were potent inhibitors of dihydrofolate reductase (23), these in vivo and related studies suggested that aminopterin acts as an essentially irreversible inhibitor for an enzyme system "A" involved in the conversion of folic acid to a substance with CF activity (fig 1) (22). This action appeared to be not only irreversible, but extremely rapid. The 1-hour interval which permits protection by folic acid against aminopterin toxicity appeared to be the time during which the metabolic conversion of folic acid to a CF product occurred, with resultant competitive action of CF for an enzyme system "B." It was further suggested that the inhibition of enzyme system "B" by aminopterin was not strictly competitive, even though a linear relationship was observed between the LD50 of aminopterin and the dose of CF on simultaneous administration of the drugs. It was indicated that aminopterin is a slowly acting irreversible inhibitor of enzyme system "B" and that CF interferes with the reaction of aminopterin with enzyme "B." This type of competitive relationship has been referred to as "interference" (24). More current concepts pertaining to competition for transport by a common carrier mechanism for 5-methyltetrahydrofolate, 5-formyltetrahydrofolate (CF), and MTX, with a different carrier mechanism involved in the transport of folate (25–27), could underly the above competitive relationships between CF and antifolics. Alternatively, the folic acid antagonists may indeed have some additional enzymatic inhibitory action at loci other than dihydrofolate reductase. Borsa and Whitmore (28) have proposed as an additional site of action of MTX the direct inhibition of the enzyme thymidylate synthetase.

TABLE 4.—Influence of delayed administration of CF on the toxicity of aminopterin (*from* ref 22)

Time of administration of CF relative to aminopterin (hrs after aminopterin)	Aminopterin LD50 (mg/kg) with—	
	CF at 7.5 mg/kg	CF at 75 mg/kg
0	29	
+1	27	
+3	24	
+8	7	
+24	8	17
+48	6	
Aminopterin alone	4.5	

The in vivo relationships were then investigated in animals bearing L1210 leukemia (29,30). For equivalent cost (probit) in drug-dose mortality, ami-

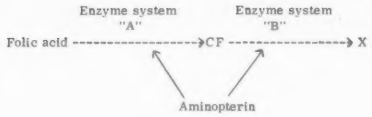

FIGURE 1.—Schema representing the metabolic transformations involving folic acid and CF, and the relationship of aminopterin thereto (*from* ref 22).

nopterin alone was more effective in increasing the survival time of animals that died from leukemia than aminopterin plus concomitantly administered CF (table 5) (30) or aminopterin plus FA^{-1}. Thus, despite the ability to use higher dosage of aminopterin, the protection afforded by CF administered concomitantly or FA^{-1} was proportionately more effective for the host than for the tumor so that there was a net loss in therapeutic effectiveness.

In contrast, in 1954, we observed that when CF was administered 12–24 hours following aminopterin, for equivalent probit of toxic mortality, aminopterin plus CF was more effective than aminopterin alone in increasing the survival time of the leukemic mice (table 5) (30).

Thus, with the delayed administration of CF, the CF reduced the toxicity of aminopterin for the host but did not reduce its antileukemic effectiveness. As a result of this it was possible to employ higher dosages of aminopterin with the delayed CF and to thereby obtain an improved therapeutic response.

Thus, overall, the administration of a metabolite with an antimetabolite could indeed result in a net increase in the specificity of action of an antileukemic agent.

A second factor that was determined to influence the specificity of action of an antileukemic agent was the dosage schedule. In 1954 (31), it was observed that an intermittent treatment schedule of aminopterin on Days 2 and 6 following leukemic inoculation provided increased antileukemic effectiveness by virtue of the ability to employ a higher total dosage of drug.

In 1955 (32), a study was conducted to investigate whether the two methods for increasing the antileukemic specificity of action of aminopterin, ie, a delayed administration of CF and an intermittent schedule, would supplement each other. It was observed that at equal cost in drug-dose toxicity, treatment on Days 2 and 6 plus delayed administration of CF (12-hour delay following each dose of aminopterin) was more effective than the intermittent schedule alone or single treatments plus delayed administration of CF (table 5) (32). The advantage in therapy, again, resulted from the ability to achieve a higher dosage of the drug (aminopterin) using the intermittent schedule plus delayed administration of CF.

Also in 1955 (33), MTX was found to be more effective than aminopterin in the treatment of L1210 leukemia on several schedules of therapy. Further, with two treatments with MTX spaced 4 days apart (Days 2 and 6) after leukemic inoculation, compared with daily treatment on Days 2–6, it was possible to employ a considerably higher dosage of the drug and thereby to achieve a more extensive therapeutic effect. With MTX, as with aminopterin, on the intermittent 4-day therapy schedule there was evidently proportionately greater recovery with

TABLE 5.—Effect of concomitant and of delayed administration of CF on the therapeutic effectiveness of aminopterin in mice with L1210 leukemia (*from* refs 30,32)*

Treatment	Mean survival time (days)	% increase in survival time relative to untreated controls
Control	15.2	
200 mg/kg of CF concomitant with aminopterin	18.6	22.4
Aminopterin alone	19.6	28.9
Aminopterin + 200 mg/kg of CF delayed 24 hrs	21.6	42.1
Aminopterin + 200 mg/kg of CF delayed 12 hrs	22.3	46.7
Control	15.3	
Aminopterin on Day 6 + CF delayed 12 hrs	20.4	33.3
Aminopterin on Day 2 + CF delayed 12 hrs	20.5	34.0
Aminopterin on Days 2 + 6 + CF delayed 12 hrs	23.9	56.2

*Comparison at equal calculated probit (cost) in drug-dose mortality.

respect to host toxicity than with respect to recovery of leukemic growth, compared with the daily treatment schedule.

In addition, in 1955 (34), studies were conducted on long-term intermittent therapy with aminopterin and MTX, with and without delayed administration of CF, in the management of mouse L1210 leukemia. The protocols all involved high-dose therapy. MTX and MTX plus delayed administration of CF were more effective than aminopterin alone or aminopterin plus delayed CF. In this study continuous intermittent therapy with MTX alone and MTX plus delayed CF was highly effective in increasing the survival time of the animals, and there was also a moderate cure rate. Overall, the use of delayed CF resulted in the achievement of somewhat more extensive antileukemic action.

Additional studies were conducted in 1966 (35) in a comparison of the ability of MTX and MTX plus delayed CF to eradicate L1210 leukemic cells. It was observed that there was a definitive increase in the margin of safety for MTX when it was used with delayed administration of CF. There was a reduction in the risk of lethal toxicity for a selected dose of MTX, but therapeutic effectiveness was retained. Higher doses of MTX could then be used with delayed CF and there was an increase in the percentage of animals cured of leukemia.

The gastrointestinal toxicity of MTX in the clinic has been well documented (36). In 1970 (37), it was observed that administration of CF orally in normal and leukemic (L1210) mice prevented toxicity and gastrointestinal lesions resulting from administration of high doses of MTX. However, the therapeutic advantage was maintained.

The primary ways, then, in which it has been possible to increase the dosage of MTX have been:

(*a*) Use of appropriate scheduling of therapy. The scheduling modalities may involve the number of treatments, the interval between treatments, and the total duration of treatment.

(*b*) Use of a metabolite such as CF in a way in which the toxicity for the host may be controlled, without undue loss of therapeutic effectiveness.

(*c*) Combination of the scheduling approach and the delayed CF approach, to obtain further increases in activity.

There was considerable delay in the transfer of the preclinical observations to the clinic. Nevertheless, there has been some correspondence of the results of animal and clinical therapeutic investigations with high-dose MTX regimens. Condit and Eliel in 1960 (38) and Perrin et al in 1963 (39) demonstrated the therapeutic efficacy of high intermittent doses of MTX in the remission induction of acute lymphocytic leukemia. In 1965, Selawry et al (40) reported that intermittent treatment with MTX was more effective than daily treatment in the prolongation of remission maintenance and lifespan of children with acute lymphocytic leukemia. Sullivan et al in 1959 (41) used intra-arterial infusions of MTX with concomitant im administration of CF. In 1966, Djerassi et al (42) reported long-term remissions in childhood acute leukemia with infrequent infusions of MTX plus supportive platelet transfusions and CF. In a series of studies initiated in 1967 (43–47), Bertino and his colleagues emphasized the concept of high-dose MTX and CF rescue in the treatment of patients with leukemia and solid tumors.

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ANNOUNCEMENTS

Seminars in Oncology at Roswell Park Memorial Institute

Buffalo, New York

There will be a seminar on "Adolescent Oncology" on April 12, 1978, organized by the Department of Cancer Control and Rehabilitation. The chairperson is Dr. H. James Wallace, Jr.

There is a $10.00 registration fee. *For further information contact:* Ms. Claudia Lee, Cancer Control, Roswell Park Memorial Institute, 666 Elm St, Buffalo, NY 14263.

Third Annual "Symposium on Advances in Cancer Treatment Research"

Baltimore, Maryland, May 18–20, 1978

The Baltimore Cancer Research Center, The National Cancer Institute, and the Program of Continuing Education of the University of Maryland School of Medicine are pleased to announce their Third Annual "Symposium on Advances in Cancer Treatment Research" to be conducted in Baltimore, Maryland, May 18–20, 1978, at the Baltimore Hilton Hotel.

An experienced and internationally recognized faculty will participate. This symposium is designed to update physicians and surgeons in some of the most recent developments in cancer treatment and current research including areas of clinical management, etiology, and cellular biology. Faculty members will be available throughout the symposium to discuss any questions or interests of individual course registrants. A visit to the Baltimore Cancer Research Center can be scheduled for interested persons. This course is accredited for 16 hours of Category 1 credit for the PRA of the AMA by the Program of Continuing Education, University of Maryland School of Medicine.

For further information please contact: Jack Mason, PhD, Assistant Dean for Continuing Education, 655 W Baltimore St, Baltimore, Md 21201, phone (301) 528-7422.

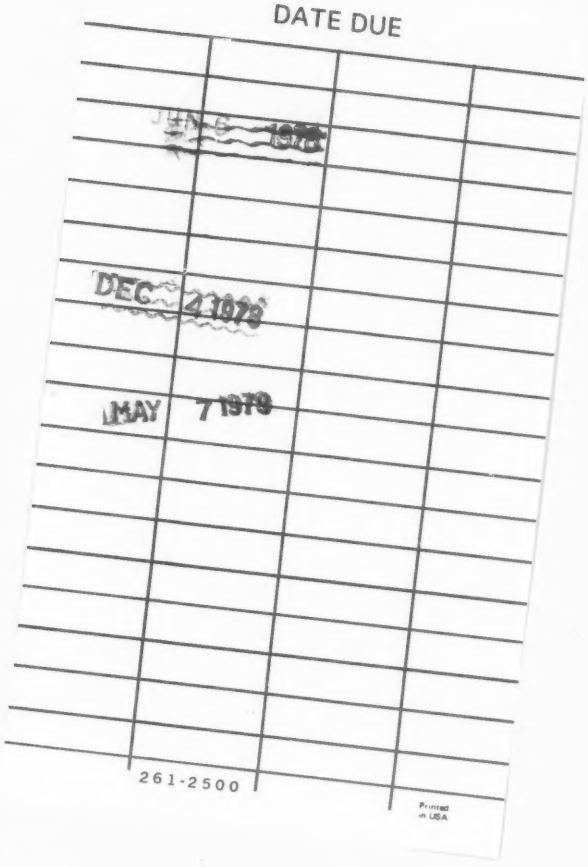
23rd Annual Clinical Conference on "Cancer of the Genitourinary Tract"

Houston, Texas, November 2–3, 1978

The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute in Houston, announces the 1978 Clinical Conference on "Cancer of the Genitourinary Tract" to be held at the Shamrock Hilton Hotel, Houston, Texas, November 2–3, 1978. This Conference will focus on issues of diagnosis, staging, and therapy as they relate to the critical and sometimes controversial therapies for the multiple stages of urologic malignancies. The Conference will be jointly sponsored by The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, and the American Cancer Society, Texas Division, Inc. It will provide practicing primary-care physicians, oncologists, and urologists with critical issues at the moving edge of therapeutic investigation of urologic malignancies. An opportunity will be provided for speakers and registrants to exchange information at the conclusion of each session. There will be a registration fee.

This medical-education offering meets the criteria for 14 hours in Category I of the Physician's Recognition Award of the American Medical Association. This program is also acceptable for 14 prescribed hours by the American Academy of Family Physicians.

For additional information write: George R. Blumenschein, MD, Office of Education, The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Texas Medical Center, Houston, Tex 77030.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